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Council on Pharmacy
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OF THE

COUNCIL ON PHARMACY AND
CHEMISTRY

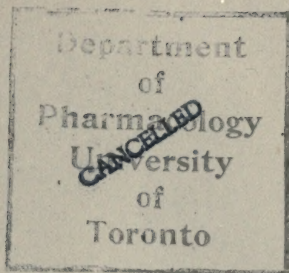
OF THE

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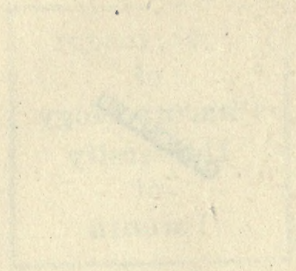
COMMENTS THAT APPEARED IN
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PREFACE

The reports of the Council on Pharmacy and Chemistry of the American Medical Association have appeared from time to time in more or less complete form in *The Journal of the American Medical Association*. The more technical and scientific parts of the reports, however, in some cases, both from lack of space and because of their technical nature, have been abstracted or entirely omitted from the published reports. Believing that these scientific investigations should be available to scientists in general, especially to chemists, pharmacologists, etc., interested in medicine, this volume, containing the complete reports of the Council for 1910, as well as the comments which appeared at the time of publication, has been prepared.



PREFACE

The purpose of this book is to present a summary of the work of the American Medical Association in the field of public health. It is intended to be a guide for the physician and the layman alike. The book is divided into two parts. The first part is devoted to a description of the work of the American Medical Association in the field of public health. The second part is devoted to a description of the work of the American Medical Association in the field of medicine.

PRESS OF
AMERICAN MEDICAL ASSOCIATION
FIVE HUNDRED AND THIRTY-FIVE DEARBORN AVENUE
1911

This book is a summary of the work of the American Medical Association in the field of public health. It is intended to be a guide for the physician and the layman alike. The book is divided into two parts. The first part is devoted to a description of the work of the American Medical Association in the field of public health. The second part is devoted to a description of the work of the American Medical Association in the field of medicine.

Report of the Council on Pharmacy and Chemistry

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Reports of the Council on Pharmacy and Chemistry

CURARE

Report to the Council on Pharmacy and Chemistry

(From The Journal A. M. A., Jan. 15, 1910)

Physiologically, curare is an exceedingly active drug; its therapeutic value, however, in the opinion of the Council, is largely hypothetical. Added to this is the impossibility of obtaining pure material of definite action and the confusion that exists in regard to the names of the alkaloid obtained from different kinds of curare. For these reasons, the Council has voted that curare and curarin be not described in New and Nonofficial Remedies, but in view of the fact that these drugs are often referred to in medical literature it is thought advisable to publish the following general article.

W. A. PUCKNER, Secretary.

CURARE

Under the name curare several varieties of native extracts used as arrow poisons are known. These are commonly indicated by the kind of container in which they come into commerce, and are called calabash curare, tube curare (coming in bamboo), and pot or jar curare (German Topf).

The calabash curare is obtained principally from *Strychnos toxifera*, and contains the alkaloid curarin: the tube curare, or tubocurare, is from an undetermined source, it yields the alkaloids, tubocurarin and curin; the third variety of curare coming in jars is obtainable chiefly from *Strychnos Castelnovi* and *Cocculus toxiferus* and contains the alkaloids protocurarin and protocurin. Curare is variously called urari, woorari and woorall.

The method of preparation is not known. The various curares are found in brown masses of an intensely bitter taste not wholly soluble in water but much more soluble in dilute acid.

Action and Uses.—Curare paralyzes the endings of motor nerves in striped muscles in the following order: (a) short muscles of the toes, ears and eyes; (b) limbs, head, and neck; (c) respiration; (d) the heart, which is not affected except with very large doses. The paralysis does not affect the sensory nerves. In warm-blooded animals death occurs from paralysis of the respiration, convulsive movements sometimes occur and glycosuria is occasionally produced. In man

little or no effect is produced when it is administered by the mouth.

Small hypodermic doses increase the force and the frequency of the pulse, raise the temperature slightly and cause perspiration and an increase in quantity of the urine. From larger quantities of the poison violent febrile phenomena occur, commencing with the characteristic symptoms of a severe chill.

Paralysis of the lower extremities comes on and may last from a few minutes to an hour. The fever may continue for 5 or 6 days if the dose is larger. Curare has been used but with little success in the treatment of tetanus and other conditions in which convulsions are prominent, and for this purpose it may be injected subcutaneously.

Curare should be used only after the specimen has been tested and the dose should be calculated as follows: The fatal dose per kilogram of dog is determined and one-tenth of this amount is administered for each kilogram of weight of the patient. This dose may be cautiously increased until there is some interference with respiration if care be taken not to induce total paralysis of respiration and if preparation has been made to carry on efficient respiration if it should become necessary.

Dosage.—The exact dose cannot be stated, as will be understood from what has been said, but the crude extract is somewhat variable in activity, and it would seem to be much better to use only the pure alkaloid curarin for therapeutic purposes. Physostigmin is the physiologic antidote—but artificial respiration must be the main dependence.

CURARIN

Curarin ($C_{10}H_{24}N_2O$), is the alkaloid prepared from calabash curare.¹

1. This is prepared from calabash curare as follows: The finely powdered curare is macerated for some days with successive portions of water and then with diluted sulphuric acid. The mixed filtrates are treated with platinum chlorid so long as any precipitation occurs, the voluminous clay-colored residue is filtered through hard filter paper with pressure and washed with alcohol. The residue is transferred to absolute alcohol, heated on a water bath and decomposed by a stream of hydrogen sulphid, adding alcoholic ammonia from time to time to neutralize the liberated hydrochloric acid. Decomposition is complete in half an hour usually if the temperature is maintained sufficiently high, but the reaction does not take place in the cold. The mixture is filtered and the residue washed with absolute alcohol. Ether is added to the dark, red-brown filtrate to precipitate the curarin. The voluminous, flesh-colored, flaky, precipitated alkaloid is quickly collected on a filter, washed with ether and transferred to a desiccator wherein it becomes a slightly colored powder.

This impure product containing sulphur and inorganic salts is purified by treating it with a mixture of chloroform and absolute alcohol and filtering. The residue is dissolved in absolute alcohol and again precipitated with ether and the residue treated as before. This must be repeated until 0.34 milligrammes of the product

Action and Uses.—The pharmacologic action of curarin has been described under curare, but mention should be made of certain differences between the several alkaloids found in the different varieties of curare. Curarin first paralyzes the motor nerve endings without affecting the heart and blood pressure to an important degree.

Tubocurarin has a very much weaker action on the motor nerve endings than has curarin. It first stimulates the reflex excitability of the cord which it later depresses. It also has a much greater effect on the heart, increasing the rate. The increased reflex irritability may persist with small doses. Curin does not participate in the action of curarin on the motor nerve endings but acts directly on the heart, first increasing the systole then depressing it; the heart finally stops in diastole after fatal doses.

Protocurarin acts qualitatively like curarin, but it is more active. Curarin is used for the same purposes as curare, but it has the advantage of being more constant in its action.

Dosage.—Curarin is used therapeutically only for its action on the motor nerve-endings and the dose must be very carefully regulated by the effects. From one to twelve milligrammes are injected for a man. The dose should be cautiously pushed until the extremities are motionless. The means for carrying on artificial respiration must be at hand, and if the respiration is seriously impaired artificial respiration must be carried on. The drug is very rapidly excreted by the kidneys and natural respiration is soon restored if the dose has not been excessive. The heart must also be carefully watched.

Owing to the differences in physiologic action between the curarins of different origin it is unfortunate that a manufacturer should give tubocurarin as a synonym for curarin.

will kill one kilogramme of rabbit, but this degree of toxicity is often attained after the first drying. (Boehm. Arch. der. Pharm., cccxxv, 660.)

Tubocurarin ($C_{19}H_{31}NO_4$) from tubo-curare, is given as a synonym for curarin by Merck, although the action of the two is not the same. Tubocurarin is prepared as follows: An aqueous or slightly acid solution of curare is made slightly alkaline by ammonia causing a precipitate to be formed. This is separated from the solution which is now free from curin, another principle of curare. The solution is evaporated to a thin syrupy consistence and mixed with 2 volumes of alcohol and the clear solution precipitated with alcoholic solution of mercuric chlorid. The yellow flocculent precipitate thus formed is suspended in alcohol and treated with hydrogen sulphid to liberate the base from the mercury. The filtrate from this operation is treated with 3 volumes of ether, thereby precipitating the hydrochlorid of tubocurarin. This product is washed and dissolved in 96 per cent. alcohol and precipitated by the addition of 5 volumes of ether. From the hydrochlorid the free base can be prepared.

Curarin is a deliquescent powder soluble in water and alcohol (Merck). Oxidized by potassium permanganate it yields amines and oxalic acid. In general it has the properties of a quaternary base. It has a bitter taste.

CONCLUSIONS

1. Curare is a powerful and dangerous respiratory and cardiac depressant and paralyzant of motor nerve endings in striped muscle.

2. The value of curare either in tetanus or in any other disease is questionable.

3. No dose can be stated. The antidote, physostigmin, must be at hand and one must be ready to perform artificial respiration after each administration.

4. Each of the several alkaloids from the three varieties of curare has a different strength and a somewhat different action.

5. These alkaloids are not at present sufficiently differentiated in commerce to enable a physician to know which one he is using.

UNICORN ROOT, WILD YAM AND WILD INDIGO**Report of the Council on Pharmacy and Chemistry**

(From The Journal A. M. A., Jan. 22, 1910)

The Council has voted that recognition be refused to the following: Unicorn Root (*Aletris farinosa*). Wild Yam (*Dioscorea villosa*), and Wild Indigo (*Baptisia tinctoria*) and has authorized the publication of the following statements.

W. A. PUCKNER, Secretary.

UNICORN ROOT—ALETRIS FARINOSA

Unicorn Root (*Aletris farinosa*) contains a bitter principle and starch. Remarkable powers as a uterine tonic have been ascribed to it but have not been realized by reliable observers, the drug being practically valueless in these conditions. It enters into the composition of a number of nostrums. As a bitter it is superfluous and it should not be included among non-official drugs.

WILD YAM—DIOSCOREA VILLOSA

Wild Yam (*Dioscorea villosa*) has been little used in medicine. It contains a saponin and an acrid resin, and is said to possess expectorant, diaphoretic and—in large doses—emetic properties. It has been recommended as a remedy in biliary colic and in muscular rheumatism. Its value in such conditions has not been verified to an extent entitling it to consideration as a useful remedy.

WILD INDIGO—BAPTISIA TINCTORIA

Wild Indigo (*Baptisia tinctoria*) has been in use—chiefly by the eclectics—for about three-quarters of a century, but there

is no satisfactory evidence that it has any therapeutic value. The following text-books on pharmacology do not even mention wild indigo: Cushny, Brunton, Dixon, Binz, Sollmann. It is not official in the United States or other leading pharmacopias.

A preparation of wild indigo is advertised with extravagant claims for its therapeutic action, but these claims are not supported by any substantial evidence. Other virtues ascribed to wild indigo are its properties as a cardiac and hepatic stimulant and its value in sepsis, particularly in typhoid fever. It actually has emetic and cathartic properties, but even these are inferior to those possessed by many other drugs.

It is very evident that a drug possessing the extraordinary merits that have been claimed for wild indigo would not have remained unnoticed by the leading authorities on pharmacology and therapeutics, especially after its prolonged use in medicine. Owing, therefore, to the lack of substantial evidence of its usefulness, baptisia is not considered as of sufficient importance to warrant its inclusion in the list of non-official drugs. It is probably entirely superfluous.

SCOPOLAMIN AND MORPHIN IN NARCOSIS AND IN CHILDBIRTH

Report to the Council on Pharmacy and Chemistry

(From *The Journal A. M. A.*, Feb. 5 and Feb. 12, 1910)

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[The following report was submitted to the Council on Pharmacy and Chemistry of the American Medical Association, which authorized its publication.

W. A. PUCKNER, Secretary.]

E. Schmidt isolated scopolamin from several solanaceous plants and described it about ten years after Ladenburg had obtained hyoscin from the mother liquors in the manufacture of hyoscyamin. Schmidt's studies were more complete and exact than those of Ladenburg, and the name scopolamin is now applied correctly to the substance for which Schmidt first gave the true formula, $C_{17}H_{21}NO_4$, Ladenburg having given the formula for

hyoscin, incorrectly, as $C_{17}H_{23}NO_3$. The term scopolamin was at first applied to levo-rotary hyoscin by Schmidt, while Hesse called the racemic form atropin, and this term is still used commercially by Merck.

The scopolamin, or hyoscin, sold was often impure, and, since different individuals showed marked differences in reaction even to the pure substance, dependent on a variety of conditions which will be discussed later, certain investigators maintained for a time that scopolamin and hyoscin were not identical, at least in physiologic action, but this question may be considered as definitely settled now, and chemists and pharmacologists agree that scopolamin and hyoscin are identical, and it may be taken that whatever is said here concerning scopolamin is intended to apply equally to hyoscin.¹

The abuse of scopolamin in anesthesia has arisen largely through a misunderstanding of its pharmacologic action, and, since an understanding of these actions is essential to a comprehension of the question at issue, they will be summarized briefly before the general question of the use of scopolamin and morphin in anesthesia is considered.

PHARMACOLOGIC ACTIONS

Kobert² states that scopolamin exists in the optically active and inactive forms. Large doses act like atropin on the pupil, accommodation, skin, heart, lungs, intestines and on all glands, but quite small (therapeutic) doses have a different action; thus the vagus is slightly stimulated, not depressed, and the pulse rate is therefore slowed, and only after large doses is there vagus paralysis. Small doses abolish cerebral excitement, this narcotic action being so strong that the maximal dose at first was placed at 0.5 milligram (1/130 grain) in all countries, but now, unfortunately, and without sufficient reason, this amount has been doubled. Kobert believes this larger dose to be applicable to the optically inactive form alone.

1. For a discussion of this point, see THE JOURNAL, Dec. 21, 1907, p. 2103.

2. *Pharmakotherapie*, Second ed., p. 481.

Kochmann states that small doses stimulate the vasomotor center, with a rise of blood-pressure and little change in the pulse rate; large doses cause a fall of blood-pressure from injury to the excitomotor apparatus in the heart. Moderate doses cause vagus paralysis in the rabbit, but this does not follow the use of even large doses in the dog. He states that scopolamin has no sedative action on the rabbit, while in man and the dog it induces sleep without analgesia.

Normal dogs survived enormous doses of scopolamin, and only those which had been previously injured succumbed. Normal frogs could not be killed by the largest doses.³ The rabbit exhibits primary paralysis of respiration, as man does, but man suffers no injury from therapeutic doses. Scopolamin is excreted by the kidneys.

These results of Kochmann's are confirmed for the greater part by Kionka (1908), but his results with dogs were slightly different, in that Kionka observed some analgesia and two distinct types of action, some becoming somnolent at once, while others exhibited restlessness, incoordination, hallucinations and sank to sleep gradually.

Kionka also tested the solutions which Kochmann had used two years previously and found no quantitative or qualitative differences in physiologic action, though the optically active had become optically inactive. Kionka also compared the physiologic actions of optically active and inactive scopolamin in freshly prepared solutions and could detect no essential difference between them, but differences were seen in the actions of the same specimen of scopolamin on different individuals of the same species. These differences in individuals were perceptible in the frog, and, becoming more pronounced with the cerebral development of the species,

3. Githens reported a case in which $\frac{4}{5}$ of a grain (52 mg.) of scopolamin had been taken at one dose without injury. The results in this case have been widely quoted, but the evidence concerning the actual dose is circumstantial, the patient having taken all that was left after previously using some of the solution. The solution was not sterile and it had been kept standing for some time. Finally, the precise quantity originally present in the bottle is not vouched for by Githens.

were more marked in the dog than in the rabbit, and, of course, attained their maximum in man.

Ernst perfused the spleen and kidney with solutions of scopolamin of various concentrations, but there were no constant effects on the blood vessels in the series of twenty-two perfusions. Cushny found that levo-rotary hyoscin acts twice as energetically as the racemic form on the terminations of the secretory fibers in the salivary glands and on the inhibitory fibers in the heart, but that they act alike on the central nervous system in man and other mammals, and on the terminations of the motor nerves in the frog, but that they do not act on the central nervous system of the frog even with the largest doses.

The physiologic actions of morphin are so well known that they do not require exhaustive discussion here.

Schneiderlin, Korff and Blos were the earliest advocates of the use of scopolamin and morphin in narcosis, and their statements of the physiologic actions and antagonisms of these two alkaloids have been summarized by Kochmann about as follows:

1. Morphin slows the pulse; scopolamin increases the rate.
2. Morphin slows the respiration and renders it shallow; scopolamin causes it to become deeper and quicker.
3. Morphin paralyzes sensory nerves; scopolamin paralyzes the motor.
4. Morphin induces miosis; scopolamin, mydriasis.
5. Morphin is a vasodilator; scopolamin, a vasoconstrictor.
6. Morphin leaves the secretions unchanged; scopolamin paralyzes them.

The synergistic action in narcosis and the wide-spread antagonisms of side actions have been the chief arguments used by Schneiderlin and Blos in support of their claims concerning the value of the combination, but it is hardly necessary to say that the antagonisms are more apparent than real, or that they are in part purely imaginary. Thus, while morphin is, indeed, a miotic and scopolamin a mydriatic, the action of morphin is purely a central one, while the mydriatic action of scopolamin is purely peripheral. As to the paralysis of

the sensory endings, it may be said that there is no evidence in the literature of any such action from morphin, and, on the contrary, it is well known that its analgesic action is purely central, while the paralysis of motor endings by available doses of scopolamin occurs only to a very limited extent, and then to the detriment of the heart.

There is no antagonism between scopolamin and morphin on the respiration in the doses often used by Schneiderlin, Korff and Bloss. The effects of morphin on the circulation, according to Sollmann,⁴ are complicated and variable and of but little importance, as they are pronounced only with very large doses. The effects of scopolamin and morphin on the pulse rate are alike quite as often as they are unlike.

Since the recommendation of scopolamin with morphin was based on such a complete misconception of true conditions, it is not surprising that, after the sacrifice of perhaps thirty lives (and just how many no one can say positively), we are back to almost the identical position in which we should have been but for the unfortunate enthusiasm of the early advocates of this combination; i. e., its use preliminary to inhalation anesthesia—precisely the object which Schneiderlin had in view when he administered the very first dose.

Those who wish to pursue this phase of the question are referred to the papers of Kochmann, Kionka, H. C. Wood, Jr., Cushny, de Stella and others who have studied the pharmacologic actions of these two drugs.

Schneiderlin was led by his observations of the effects of scopolamin on the insane to use scopolamin and morphin for the purpose of reducing to the minimum the amount of chloroform required for anesthesia in the case of a patient suffering from carcinoma of the breast. The results so far exceeded his expectations that he experimented further and found that scopolamin and morphin alone sufficed in some cases for light anesthesia. He gave amounts up to 2.5 milligrams ($1/25$ grain) of scopolamin and 7 centigrams ($1\frac{1}{6}$ grains) of morphin in the space of an hour and fifteen minutes.

4. Text-book of Pharmacology, Second ed., p. 186.

Although he found the effects of scopolamin variable and his observations extended only to some ten cases, he drew rather broad deductions, concluding that scopolamin and morphin are not dangerous; that the unforeseen accidents of chloroform inhalation were thereby avoidable; that the constant attendance of the physician is unnecessary, merely an attendant to be at hand in case the tongue should fall back into the throat and the respiration cease; the condition of the pupils was urged as a guide to the administration of the two drugs, than which, as we have seen, nothing could be more fallacious.

This paper of Schneiderlin's is not readily accessible to the general reader, in this country at least, and it is remarkable how considerably the average critic has dealt with Schneiderlin's reasoning and deductions.

I believe that we should be inclined to consider as little less than reckless one who would pronounce a new anesthetic harmless, because ten patients had survived its administration. Apparently Schneiderlin had no idea of its possibilities for degenerative changes on the internal organs. He even went so far as to advise initial doses of 1 milligram of scopolamin and 3 centigrams of morphin if in haste to operate. It must be said, in justice to Schneiderlin, that he did not pretend to have perfected the technic of scopolamin-morphin anesthesia.

Schneiderlin's truly remarkable announcement was soon followed by observations by other surgeons. Bloss took up the investigation within a month of the appearance of Schneiderlin's paper and about two years later he published his results in 105 cases. Bloss repeats the fallacious statements made by Schneiderlin concerning the antagonistic actions of the two alkaloids, and, despite one death in his series, which he attributed to an accident that could be avoided thereafter, he commended the method warmly. Bloss gave even more morphin than Schneiderlin had done—up to 12 centigrams (2 grains) in two portions—and was more enthusiastic in his praise of the combination. In this connection it is interesting to note that about three years later Bloss

wrote to de Maurans, stating that he rarely used the method after leaving the hospital.

Korff reported on 80 cases in which he used scopolamin and morphin, employing doses of 1.2 milligrams ($1/50$ grain) of scopolamin and 3 centigrams ($1/2$ grain) of morphin in three portions of 0.4 milligram ($1/150$ grain) scopolamin and 1 centigram ($1/6$ grain) morphin each. Korff modified this dose somewhat after about a year, but still adhered to doses that have been abandoned by conservative surgeons. The use of such a dangerous combination could hardly fail to cause a number of deaths, and there was the inevitable reaction, many abandoned the method altogether, while others continued to use it in a modified form.

Disregarding the early methods, which no longer obtain among well-informed surgeons, but which are considered in order to gain a better understanding of the question, we will discuss the use of scopolamin and morphin preliminary to general anesthesia and to induce the so-called twilight sleep in obstetrics.

SURGICAL USES

The principal advantages and disadvantages have been observed by numerous investigators, and it is useless to enumerate these observations in each case. Therefore the opinions of the majority are considered collectively, except when it may be necessary to call attention to opposing views.

ADVANTAGES

The advantages which can be claimed conservatively for scopolamin and morphin in anesthesia may be briefly summarized as follows:

1. It permits economy of chloroform or ether, with the attendant advantages; it reinforces spinal anesthesia.
2. There is lessened postoperative nausea and emesis, with the decreased danger of pneumonia and other side-actions.
3. The stage of excitement is lessened or abolished, and the fear of anesthesia is eliminated largely.

4. The course of anesthesia is rendered smoother and more uniform.

5. There is decreased salivation after ether and a diminution of pneumonia.

6. There is sleep of some hours following operation, with the avoidance of pain which commonly follows operations with chloroform or ether.

7. In addition to those mentioned, there are minor advantages which will be mentioned later.

1. *Economy of Chloroform and Ether.*—It is claimed by a very large majority of observers that scopolamin and morphin effect an economy of chloroform and ether. While this is a matter of prime importance, it is so purely a surgical question that it cannot be considered exhaustively here, but the following citations illustrate the point: Zadro (1909) states that 60 grams (2 ounces) of Billroth's mixture and 100 grams of ether suffice for an operation of an hour, but with 0.5 milligram ($1/130$ grain) of scopolamin and 1 centigram ($1/6$ grain) of morphin, 25 grams ($5/6$ ounce) of Billroth's mixture and 80 grams ($2\frac{2}{3}$ ounces) of ether, or 120 grams (4 ounces) of ether, suffice. Among others who report economy of ether is Flatau, who states that this economy is not attended with lessened emesis. Schoemaker (1909) reports that he found no marked economy of chloroform or ether, but he admits that these act less injuriously after scopolamin and morphin. If the latter statement is correct, we must conclude that less than usual of chloroform and ether were actually used.

2. *Lessened Nausea and Emesis.*—Blos states that patients take food almost immediately after an operation following the use of scopolamin and morphin, and that recovery is rapid in consequence. Several observers state that patients look fresher and better than after chloroform or ether alone. Hartog (93 cases) states that nearly all patients show an extraordinary good condition after operation following the use of scopolamin and morphin, and Klein remarks that such patients recover quicker and better than after long chloroform narcosis alone. A great majority of observers report

that there is less emesis immediately following operations, with scopolamin and morphin, than with chloroform or ether alone.

The disadvantages and dangers of this postoperative emesis do not require detailed discussion here, but, in addition to the fatal pneumonia, which it causes so often, there are many minor disadvantages resulting from it. Flatau says that postoperative emesis is often the cause of hernia as well as hemorrhage. Blos calls attention to the increased viscosity of the blood commonly resulting from emesis and the inability to take water. Korff claims that the ability to take food soon after an operation greatly lessens the danger of hemorrhage, and that many stitches are pulled out during emesis. The ability to take food soon after an operation certainly hastens repair and increases the resistance to infection.

The testimony is conflicting in regard to the actual frequency of emesis after operations following scopolamin and chloroform or ether, but the real benefits of scopolamin and morphin in this respect cannot be shown by tables giving merely the frequency of emesis; the interval before its occurrence is of even greater importance. This is illustrated strikingly in Ries' report. Ries states that emesis occurred in about 60 per cent. of his cases in which chloroform was used after scopolamin and morphin, and in about 36 per cent. of those where ether followed, but only once in the series of 185 major operations did emesis occur within twenty-four hours, and he did not have a single case of pneumonia in the entire series.

As to the actual frequency of emesis after scopolamin and morphin and chloroform or ether, there is little doubt that it is materially decreased in the first twenty-four hours following operation, and, indeed, in the whole period concerned. Schoemaker (1909) states that there was emesis in about 10 per cent. of his 3,000 cases in which scopolamin and morphin were used, which was a marked reduction from that seen when he used chloroform or ether alone.

Flatau claims that emesis is not lessened by small doses of scopolamin and morphin, but the effective doses used by Grimm and by Schoemaker were quite small, 0.5 milligrams of scopolamin, and 1 and 1.5 centigrams of morphin, respectively, and the results obtained by Ries, previously mentioned, were obtained from the use of 0.65 milligram of scopolamin and 1.0 centigram of morphin (1/100 grain scopolamin, 1/6 grain morphin).

The lessened tendency to postoperative pneumonia after scopolamin and morphin with chlorform and ether, owing to lessened emesis and lessened salivary secretion after ether, is shown by the following figures: Boesch states that there were only 0.7 per cent. of cases of postoperative pneumonia following 2,000 operations with scopolamin and morphin and inhalation anesthesia since 1905, and even less than that of late. Zadro gives 0.9 per cent. (it should be 1 per cent.) in 770 cases against 4.8 per cent. with chloroform alone in 1908. He cites the results in Kümme's clinic, where there were 0.7 per cent. of postoperative pneumonia when scopolamin and morphin were used, against 2.5 per cent. without them. In other clinics as high as 5 per cent. of postoperative pneumonia is reported where scopolamin and morphin are not used.

Grimm reports that there were 43 cases of pneumonia with 18 deaths following 1,754 laparotomies between 1895 and 1905 when scopolamin and morphin were not used, but there were only 6 cases of pneumonia and none fatal in 839 laparotomies where scopolamin and morphin were used before inhalation anesthesia.

If the averages just given are sustained by the observations of other surgeons, there can be little doubt of the beneficial action of scopolamin and morphin in preventing postoperative pneumonia, and in that event we must consider them indispensable, despite a higher immediate mortality than with ether or chloroform alone. The foregoing does not take account of the possibility of fatty degeneration of different organs resulting from scopolamin and morphin, but that probably does not occur with small doses.

3. *Lessened Excitement.*—It is so nearly universally admitted that there is lessened excitement in the early stage of anesthesia following the use of scopolamin and morphin, that the subject may be dismissed with a few words. Sieber states that morphin alone is preferable for the purpose, and Zadro claims that there is no influence on the stage of excitement in the case of alcoholic patients, but this is denied by Grimm. Hartog reports the case of an hysterical patient in whom tonic and clonic convulsions followed the injection of scopolamin and morphin, but these subsided when anesthesia was induced by inhalation.

4. *Anesthesia Smoother.*—Zeller states that no other anesthetic produces such smooth narcosis in severe operations as scopolamin and morphin. Several observers refer to his effect of scopolamin and morphin, and those who work with dogs in laboratory experiments have noted this effect of morphin.

5. *Decreased Saliva.*—The profuse flow of saliva during the inhalation of ether is said to be a prolific source of pneumonia following its aspiration, and of emesis, from the effects of the ether in the saliva swallowed. Scopolamin checks this secretion very effectively, and it may indeed lead to extreme dryness of the mouth and throat difficulty in swallowing, intense thirst and diminished expectoration, which may prove a serious disadvantage.

6. *Long Sleep.*—Many observers mention the prolonged sleep following operations after the use of scopolamin and morphin with chloroform or ether, and state that the patient is thereby spared much suffering, which is otherwise experienced so often. Zeller states that patients often sleep from four to six hours, and Terrier and Desjardins say they may sleep as long as eight or ten hours. While this sleep is usually an advantage, there are conditions under which it may prove distinctly detrimental. Routier denies that postoperative pain is materially lessened by the use of scopolamin and morphin.

7. *Miscellaneous Advantages.*—Various individual observers mention minor advantages in addition to those already discussed, including the following: There is no mask to interfere with asepsis of the face when scopolamin and morphin are used alone for anesthesia (Blos); scopolamin and morphin anesthesia is suitable in cases in which chloroform and ether are unavailable (Dirk and others); but this is hardly borne out by what has been said of the physiologic actions of the two alkaloids and by the experience of Ely, Sexton and others. Penkert says that scopolamin and morphin “twilight sleep” and spinal anesthesia constitute the most humane method of narcosis at our disposal. Grimm is one of the few who advocates the use of scopolamin and morphin for use in general practice. Roith states that the method is more reliable than that with other anesthetics, and not more troublesome.

DISADVANTAGES

The disadvantages of scopolamin and morphin preliminary to chloroform or ether anesthesia may be summarized as follows:

1. They frequently fail to produce the desired effect.
2. They often act injuriously on the respiration and circulation.
3. There are numerous contraindications, of which many are not sufficiently defined.
4. The action is variable with different individuals.
5. They are not suited for general practice.
6. They have caused a number of fatalities.
7. There are several minor disadvantages that will be discussed later.

1. *Failure to Produce Effect.*—Nearly all observers agree that in a fairly large percentage of cases the objects sought are not attained by the use of scopolamin and morphin, whether these objects are limited to the avoidance of the stage of excitement with small doses, such as Kochmann and most observers advise, or the effort is made to economize chloroform or ether greatly, as Korff (1908) still attempts by somewhat larger doses. Twenty-five per cent of failures is probably a fair esti-

mate, but this does not apply to the prevention of post-operative pneumonia, in which, as stated, the results appear to be far better.

2. *Effects on Respiration and Circulation.*—It is well known that morphin depresses the respiration in all doses that produce any perceptible systemic action. The effects of scopolamin are, unfortunately, not so well known, and the effects of the two when combined are even less understood, though there is considerable evidence that their synergistic action in narcosis is sometimes extraordinary, in that their combined action is then much greater than the sum of their separate actions would be.

This is not a wholly anomalous condition, though it is one which is frequently overlooked. Gottlieb and Eeckhout's results with opium furnish us with an example of this peculiar synergistic action. They found that tincture of opium acts with more energy than can be accounted for by the potency of the separate alkaloids which it contains. Honigmann states that the action of a mixture of chloroform and ether is sometimes far greater than the sum of the action of the two acting separately. Wholly analogous to this is the action of atropin in antagonizing pilocarpin. Magnus states that 250 times as much atropin is required to produce stimulation when it acts alone as that required to overcome the depression from pilocarpin.

This remarkable synergy of actions has been observed on precisely those structures, i. e., those of the nervous system, in which we would expect the greater variation in reaction because of their highly specialized character, and it is with narcotics—even the identical narcotic that we have under consideration—that these peculiarities have been observed.

We are familiar with wide variations of actions, or idiosyncrasies, toward morphin, and it is possible that we are to become equally familiar with idiosyncrasies toward scopolamin. Scopolamin in large doses paralyzes the respiration, and it is apparent from the testimony of many clinical observers in cases in which death followed the use of the mixture, that the synergistic action

of scopolamin and morphin is occasionally exerted on the respiratory center in a very remarkable way. Unfortunately, we do not know the precise conditions which call forth this unusual synergistic action, but we do know that whatever tends to depress the respiratory center favors this unfortunate reaction. The respiratory depression may be direct, or it may be caused indirectly through anemia, general weakness or extremes of life.

The evidence is irrefutable that scopolamin and morphin may cause death from paralysis of respiration—a paralysis against which artificial respiration and all means of stimulation are ineffective.

Sieber (1908) stated that Hartog alone had mentioned the lasting increased pulse rate after scopolamin and morphin, but the phenomenon is mentioned frequently thereafter, and its occurrence is in accordance with de Stella's statement that toxic doses of scopolamin increase the pulse rate, and furthermore, that toxic symptoms appear and disappear rapidly. Any considerable increase in the pulse rate after scopolamin and morphin must be considered an untoward symptom unless it can be accounted for satisfactorily.

Sieber mentions a case in which the pulse rate was 80 previous to the injection of a small dose of scopolamin and morphin, but in one hour the rate was 160. The heart, lungs and kidneys were apparently sound. This case of Sieber's must be considered as very unusual, and I am not aware of any case in which a dose not exceeding 0.5 milligram ($1/130$ grain) of scopolamin and 1 centigram ($1/6$ grain) of morphin has caused the death of a patient in fairly good condition and with sound organs, but the death reported by Ely very nearly fulfills these conditions. His patient was reported to have been in good general condition, but succumbed two hours after the administration of $1/100$ grain scopolamin and $1/8$ grain morphin (0.65 mg. scopolamin; 0.8 cg. morphin). There is no better authenticated case of death from a narcotic than this one.

3 *Contraindications.*—Foremost, then, among the contraindications for the use of scopolamin and morphin are to be placed all conditions whereby the respiratory

center is depressed, or is likely to be injured directly through prolonged anesthesia, or indirectly through the circulation by shock, hemorrhage or other cause. They are certainly contraindicated in all severe cardiac diseases and other conditions which interfere with the circulation. They are available for operations for simple goiter, but nearly all authorities agree that they are contraindicated in the presence of Graves' disease, which is to be inferred from what has been said. They are contraindicated in operations about the throat and mouth, since the prolonged sleep and interference with expectoration favor the aspiration of the blood. One death has been attributed partly to this, pneumonia, due to aspiration of blood, being the immediate cause of death.

The question of special indications and of contraindications for scopolamin and morphin has probably caused more disagreement than any other in connection with the subject of their use. Sick thinks there are no contraindications, while Sieber declares that there are no indications for their use. Sieber closes his article with the following exclamation: "*Also Weg bei der Narkose mit diesem unberechenbaren, meist nutzlosen, gefährlichen Gifte*" ("Away with narcosis by this uncertain, mostly useless, dangerous poison").

Much of the controversy could have been avoided had greater attention been paid in the beginning to the physiologic actions of scopolamin and of morphin, and of the mixture acting as a unit.

4. *Variable Action.*—That the action of scopolamin and morphin is variable with different individuals follows naturally from what has been said, and it is impossible, of course, to foresee all of the conditions in man which will cause a greater or less deviation from the usual effects, and when a natural idiosyncrasy is intensified by disease or untoward conditions even small doses of scopolamin and morphin may prove fatal, as in the cases reported by Toth, Ely, Sexton and others.

These individual differences in reaction varying from no perceptible action in some cases to a fatal intoxication in others with precisely similar doses, constitute one of the greatest disadvantages of the use of scopol-

amin and morphin. Usually, however, the same patient reacts similarly at different times, but Hotz maintains that the same patient reacts differently at different times, and the possibility of this is precisely what is to be expected in view of the disturbances of the respiration and circulation which may arise, and on which the untoward results depend.

5. *General Practice.*—The method is not usually considered as suited for general practice because of the constant attention required until the action has finally worn off, as the untoward symptoms may not arise until some time after the operation. It must be considered as unsafe to leave a patient without surgical care so long as sleep continues. There is probably little danger from small doses of scopolamin and morphin for patients whose general condition is good, and who show no serious effects from the operation, but the cautious surgeon will remain within call until the patient awakens.

6. *Fatalities.*—The ultimate fate of scopolamin and morphin in anesthesia must depend largely on their relative safety as compared with other agents, particularly chloroform and ether. While this is a surgical question for the most part, it must be considered with reference to the physiologic actions of these agents if we are to arrive at a correct estimate of the value of the method, for in fatal surgical operations there are so many factors involved that it is often impossible to determine the true cause of death. But when we see a series of deaths in which the clinical observations agree with what we know of the actions of the agents in question, the evidence is certainly very much stronger than it would be if the clinical observations did not agree with those actions.

H. C. Wood, Jr., studied the cause of death in 23 cases in which scopolamin and morphin had been used, and he concluded that at least 9 of those deaths must be attributed to the scopolamin and morphin, the death rate being about 1 to 250 narcoses by this means. Roith collected statistics of 18 deaths in 4,000 cases of scopolamin and morphin narcosis, but he does not agree that scopolamin and morphin should be blamed for these

deaths. De Maurans attributed 22 deaths to these agents up to November, 1905. Viron and Morel (1906) noted 25 deaths in 2,000 cases collected from the literature.

With the methods now in vogue with the more conservative surgeons, who use only small doses of scopolamin and morphin in connection with other anesthetics, the death rate is very much lower than the figures just given would indicate, but there is no reason to suppose that better results can be obtained when scopolamin and morphin alone are relied on to induce the anesthesia.

These figures are given by way of illustration of the question of scopolamin and morphin anesthesia, and are not intended as a complete statistical study of the subject, and when statistics are considered a sharp distinction should be made between those cases in which death follows large doses of scopolamin and morphin, intended to replace chloroform or ether wholly or chiefly, and those in which only small doses of scopolamin and morphin are used for the purpose of securing freedom from excitement, lessened emesis, smoother anesthesia and freedom from some of the more annoying minor symptoms. In the light of what has been said of the pharmacology of morphin and scopolamin, it is also necessary to distinguish between the results obtained by those who use the method for all cases and those in which there is careful selection of suitable cases.

The argument has been advanced, that certain deaths following the use of scopolamin and morphin, particularly those reported by Israels, were not due to scopolamin, because there was marked fatty cardiac degeneration, but de Stella concluded that scopolamin causes widespread fatty degeneration, and Israels said he had never seen fatty degeneration from such small amounts of chloroform as had been used in those cases. Sexton's patient died within an hour and fifteen minutes of the injection of 1/6 grain of morphin (1 cg.) and 1/100 grain of scopolamin (0.65 mg.), with the usual symptoms of scopolamin intoxication, paralysis of respiration and rapid pulse. Rigidity of the muscles prevented artificial respiration in this case, but in the light of

experience in other similar cases, it would, in all probability, have done no good.

7. *Minor Disadvantages.*—Among the minor disadvantages which have been mentioned by different investigators are the following: When the morphin and scopolamin are once injected they are wholly beyond control. One surgeon writes of his emotions at seeing his patient die while he and his assistants stood by helpless to counteract the effects of the drugs they had administered.

Every additional narcotic complicates the anesthesia.

Scopolamin does not cause muscular relaxation, a disadvantage, when used with spinal anesthesia particularly, and we have seen that muscular spasm interfered with artificial respiration in one fatal case at least.

The prolonged sleep may prove a disadvantage, as already mentioned. Hirsch mentions its interference with expectoration after operations about the mouth, and it is said that the prolonged sleep and the attendant respiratory depression may favor pulmonary edema.

Intense thirst, dryness of the mouth and throat and the difficulty in swallowing are sometimes complained of by patients.

Different investigators have attempted to explain many of the accidents which occurred early in the history of scopolamin and morphin anesthesia, on the ground that the drugs employed were impure or that the solutions underwent changes whereby toxic substances were formed.

Kionka maintains that apoaotropin is the only impurity which could be concerned in the increased toxicity of the scopolamin, but he had never been able to detect this impurity in any of the specimens of scopolamin examined, hence he thought it must be extremely seldom that this impurity could be present. Apoaotropin may be detected by Kessel's method. Potassium permanganate causes a brown precipitate when one part of apoaotropin is present in 20,000 parts of the solution. Morphin and many other alkaloids give this reaction, hence it is not applicable to the mixture of scopolamin and morphin. The Swiss Pharmacopeia (1907) does not

mention this substance as an impurity in scopolamin. Kobert attributed the death of a man who had scopolamin to apoaotropin, which was said to be present as an impurity.

While solutions of scopolamin do undergo some unimportant physical changes as previously mentioned, it is probable that sterile solutions do not undergo any essential change in the course of a few months. Ries was unable to observe any difference between the effects of those solutions which had been freshly prepared and those which had been kept for some weeks. This agrees with the results of Kionka's experiments with freshly prepared, and old, solutions of scopolamin. Hotz states that milk sugar is said to prevent the deterioration of scopolamin solutions. The physical changes observed are said to be probably due to the alkali of the glass.

OBSTETRICAL USES

The discussion of the advantages and disadvantages of scopolamin and morphin in surgical practice indicates some of its uses and limitations in obstetrics, but the conditions are different in many essentials, and those relating to childbirth will be discussed independently. The physiologic actions of scopolamin and of morphin must be borne in mind here not less than in the surgical use of these agents, and there are certain points on which stress must be placed, with reference to this application of the two drugs, hence the pharmacology will be again considered briefly.

PHARMACOLOGY

Scopolamin passes across the placental circulation and appears in the first urine of the new-born child, and it is excreted into the colostrum for a variable period after its administration to the parturient woman, according to the experiments of Holzbach. Kehrer found that scopolamin caused excitation of the perfused uterus, but it is improbable that this plays an important rôle in the dose in which scopolamin is used.

Steffens states that there is normally a lowered perception in labor, and simultaneously there is central

motor irritability, which explains the increased susceptibility of the parturient woman for scopolamin. Steffens also states, as the result of experiments on himself, that the perception is not a reliable guide for the further need of scopolamin.

Scopolamin is said to be excreted fairly rapidly in the urine, but the prolonged sleep which occasionally follows its use would seem to indicate that at least a part may remain for some time in the central nervous system.

The extraordinary toxicity of morphin for the new-born child gives added importance to the questions of the behavior and of the fate of that alkaloid in the organism. Unfortunately, we are much in the dark regarding this behavior. Marquis thinks that a part of the morphin at least is destroyed by animal oxidases, and Cloetta believes that certain cells take part in its destruction, while Faust maintains that the normal animal excretes morphin unchanged. Only traces of morphin are found in the urine, the greater part being excreted into the gastrointestinal canal. It is probable that a portion of that which passes into the stomach is reabsorbed into the circulation until finally excreted by way of the intestine. Still more important, so far as the infant is concerned, is the fact that traces of morphin are excreted into the colostrum or milk, and these traces are sufficient to cause intoxication in the new-born.

Von Steinbüchel (1902) was the first to suggest the use of scopolamin and morphin in childbirth. He describes the method in his second paper, in which he gives the details of 20 cases of labor in which he used initial doses of 0.3 milligram ($1/200$ gr.) scopolamin and 1 centigram ($1/6$ gr.) of morphin, occasionally 0.4 milligram ($1/150$ gr.) scopolamin. In 3 cases there was copious hemorrhage after the child was delivered. In the earlier cases von Steinbüchel gave a second dose of scopolamin if required, not less than two hours after the first, and only one-half as large; in some of the later cases he gave the same amount in the second dose as in the first. His caution in the use of scopolamin in childbirth contrasts favorably with the boldness with which it was

used in surgery at the same period. It is by no means certain that others have succeeded in improving on von Steinbüchel's results, and his paper should be read by those who employ scopolamin and morphin in childbirth. He calls attention to the fact that the study of the problems concerned in its use cannot be pursued satisfactorily in general practice.

Gauss is given the credit usually for developing the technic of the "*Dämmer Schlaf*," or "twilight sleep," a condition which has been described as that in which perception is retained to a greater or less degree, while the memory is impaired or lost.

It is not easy to determine just what is meant by the term, however, for, after having spent six weeks in Krönig's clinic in the effort to acquire the technic, Mansfeld calls attention to the prevalent erroneous impression that the method is intended to abolish the suffering of labor, whereas it is intended only to prevent memory of the event. But six months later we find the statement made by Krönig himself that the "twilight sleep" renders childbirth almost, or entirely, painless. The title of Krönig's paper is "*Schmerzlose Entbindungen in Dämmer Schlaf*" ("Painless Labor in Twilight Sleep"). The question seems to involve the problem whether forgotten pain and painlessness are synonymous.

Gauss' technic is described in THE JOURNAL, Oct. 12, 1907, p. 1299, but Mansfeld stated that despite the four publications of Gauss' which had appeared (1908), there were many points which had not been made clear in the literature. Gauss maintains that success depends on a close adherence to the technic, but several observers who had studied this technic under Gauss report that they were unable to obtain such favorable results as he reports. This question must be left to obstetricians, but the dose and its effects require consideration.

Gauss states that rarely (1 in 1,000 cases) 0.3 milligram ($1/200$ gr.) of scopolamin and 1 centigram ($1/6$ gr.) of morphin will suffice for a case of childbirth, occasionally 1.2 milligrams ($1/50$ gr.) of scopolamin and 2 centigrams ($1/3$ gr.) of morphin will be required.

The latter dose may be borne by the woman in suitable cases without ill effects, but it is obvious from what has been said that it requires extreme care and discernment to select the cases in which such doses can be considered safe. Gauss' report appears to indicate that he has acquired the requisite skill and discernment to enable him to use the method with greater safety than other methods, but it must be remembered that we have no statistics with which to compare his records, since it is obvious that he must select the cases which are suitable. And, furthermore, as Krönig has said in answer to the complaint that the technic is too complex, that it is admittedly complex, but that it is the result of long years of study of the question.

There is practically a unanimity of opinion on this essential point, that the successful use of scopolamin and morphin in childbirth requires the utmost attention to details. It is confessedly an extremely difficult and tedious matter to secure the necessary action without overstepping the bounds of safety. The truth of this is obvious when one remembers what has been said repeatedly of the variable and uncertain action of scopolamin and the mixture with morphin. The successful use of these agents requires not only a great deal of experience and judgment in question of obstetrics, but also in the use of these particular agents in obstetrics.

Hocheisen (1906) reported on the use of scopolamin and morphin in 100 cases of labor in which the death of one child was attributed to these agents. This and numerous other disadvantages, including atonic hemorrhage and prolongation of labor, which Hocheisen urged against the method, called forth a reply from Gauss, who attributed the mishaps to a want of correct technic, but Hocheisen's paper created a profound impression, and unquestionably deterred many from using the method.

ADVANTAGES

Among the advantages claimed by the supporters of the use of scopolamin and morphin in childbirth are:

1. Memory of the event is lost.
2. Pain is lessened or abolished.
3. There is less hemorrhage.

1. *Memory Abolished.*—The testimony of the large majority of observers leaves little doubt that the woman rarely retains any memory of the labor or its suffering, and it is said that she often expresses surprise when she is told that it is over. Krönig maintains that the memory of labor is frequently the beginning of a psychosis that may be very persistent, the modern conditions of life being such that childbearing has ceased largely to be a physiologic process, and the loss of the memory of labor prevents such psychoses. If Krönig's contention is correct, the necessity for care in the use of scopolamin and morphin is even greater than it would be if labor were a purely physiologic process, for it is the normal organism which is least susceptible to these narcotics and which show dangerous symptoms seldom or not at all after small doses, but it is the abnormal animal, the one with lowered resistance, which occasionally succumbs.

2. *Lessened Pain.*—Testimony is conflicting in regard to the immediate effect of scopolamin and morphin on pain, and this is not remarkable, in view of the fact that the woman is in a semiconscious state and has an almost complete loss of memory. It seems that there is often an entire absence of pain and that more frequently the pain is greatly lessened.

3. *Lessened Hemorrhage.*—The data concerning the effects of scopolamin and morphin on postpartum hemorrhage do not suffice for a positive opinion. While Gauss observed less hemorrhage with this method than the average without it, it is impossible to say how much of the diminution is due to the technic aside from the use of scopolamin and morphin, and how much to the selection of cases. It is possible that the action of scopolamin on the uterus which Kehrer observed, may favor contraction and thereby lessen hemorrhage, but, as previously stated, this action is probably negligible with therapeutic doses.

DISADVANTAGES

While the advantages of scopolamin and morphin in childbirth are too technical for extensive consideration in this place, the disadvantages are better suited for dis-

cussion. The disadvantages include nearly all of those discussed in connection with the surgical uses of these agents, and in addition, the following are peculiar to childbirth:

1. Danger to the child.
2. Miscellaneous minor disadvantages.

1. *Danger to Child*.—The dangers to the child are due to a variety of causes, and a full consideration of them would involve a discussion of the whole problem of the use of scopolamin and morphin, for it is obvious that anything that is injurious to the mother must prove hurtful ultimately to the child.

The most immediate source of danger to the child proceeds from the action of scopolamin and morphin on the respiration. Nearly every observer reports a greater or less number of children who are asphyxial when born. It is one of the cardinal principles of medicine to avoid the use of narcotics, and particularly morphin, with infants, and it is difficult to believe that its use is wholly devoid of injurious actions. Whether the harm outweighs the benefits to the mother is a problem which cannot be answered here. Steffens maintains that the temporary interference with the infant's vital functions is by no means so harmless as Gauss supposes. Krönig maintains that this point is too abstruse for decision. Nevertheless, it is a question which we must strive to answer in the light of experience gained with a knowledge of the physiologic actions of the mixture, as well as of the separate constituents, and of the fact that the infant does not escape these actions *in utero* and immediately after birth.

A number of infants' deaths have been attributed to scopolamin and morphin, but the question involves so many points of dispute that it is impossible to say how many deaths the mixture has caused. Veit admits that the method may have certain advantages in some cases, but despite Gauss' favorable reports, Veit refused to permit any extensive trial of the method in his obstetrical clinic on the ground that it is too dangerous.

The dangers to the mother cannot be discussed here with reference to the statistics of the mortality in child-

birth, since these show wide variations. Harrar reports 114 maternal deaths in 32,000 cases of labor (1 in 280) in the outdoor obstetric service of the Lying-in Hospital in New York City, while Goldsborough reports 55 maternal deaths in 5,000 cases of labor (1 in 91) in the Johns Hopkins Hospital.

It is quite obvious that if we cannot foresee which women will manifest an idiosyncrasy toward scopolamin and morphin, the chance is still more remote that we should be able to tell which unborn child will exhibit this peculiarity. While childbirth is, or should be, a purely physiologic process, it does not follow that all parturient women are in a physiologic condition, or that all new-born children will be healthy.

2. *Minor Disadvantages.*—The drowsiness which scopolamin and morphin induce with the sleep between pains has been held to secure rest for the woman, and this rest is said to enable her to expel the child more easily because of the more effective contractions succeeding the rest (von Steinbüchel), but the testimony appears to show that at best labor is actually prolonged. This is admitted by many of even the warmest advocates of the use of scopolamin and morphin, but they maintain that the slight increase in the duration of labor is of little consequence. The prolongation of labor is attributed to lessened reflexes in the absence of pain. Whether this is in any way counteracted by the action of scopolamin on the uterus cannot be stated.

The technic of the use of scopolamin and morphin, which is universally admitted to be essential to success, depends on a variety of conditions which cannot be fulfilled in the home, hence it is stated by nearly all investigators that the method is absolutely unsuited for general practice. Krönig states, however, that it depends on whether the general practitioner is willing to take the necessary time, care and trouble to insure success.

A minor disadvantage mentioned by Hocheisen is the appearance of the woman, which is almost certain to alarm attendants who are not accustomed to the method, and their alarm tends to interfere with the very conditions necessary to the successful use of these agents.

Whatever the future of scopolamin and morphin in narcosis and in childbirth may be—and the last word has not been spoken—the true value can be determined only after experience in which the physiologic actions of the separate constituents and of the mixture acting as a unit, are kept in view.

A fixed dosage is irrational in this, as in every other form of medication. Scopolamin and morphin must not be used without reference to the physical condition of the patient, the nature of operation or probable course of labor, and due caution born of a full knowledge of the peculiar idiosyncrasies of individuals, and of the extraordinary synergistic actions that are sometimes encountered. Then, and only then, can we hope to come to any definite conclusions as to whether the advantages outweigh the disadvantages. But for the general practitioner to attempt to solve these problems in the home and under conditions, many of which alone suffice to prevent success, and many of which produce effects which cannot be estimated correctly, is to court almost certain failure.

CONCLUSIONS

1. The use of scopolamin and morphin alone, and unsupported by chloroform, ether or other anesthetic, is wholly unsuited for general anesthesia.

2. The use of scopolamin and morphin preliminary to that of chloroform or ether has certain advantages, but it renders the problem of anesthesia more complicated, requiring extreme care, judgment and discretion.

3. There are numerous contraindications to the use of scopolamin and morphin, both in surgery and in childbirth.

4. It seems probable that scopolamin and morphin may have a sphere of usefulness in childbirth, as well as in surgery, but there are many details which require perfecting before they can become generally useful even in institutions.

5. Scopolamin and morphin are wholly unsuited in the present state of our knowledge, for use in general obstetric practice.

6. The pharmacology of scopolamin and morphin, and of the interactions of the two, are of prime importance in the study of their uses in surgery and obstetrics.

7. There is no possible excuse for the employment of ready-made mixtures (pills or solutions) of scopolamin and morphin, since each substance must only be used with reference to its individual actions, bearing in mind that these actions may be greatly augmented or modified by the other alkaloid.

8. The danger to the child must be kept constantly in mind, even when the utmost care has been exercised in the selection of cases suitable for the use of scopolamin and morphin in childbirth, and when small doses are ineffective in inducing the "twilight sleep," large doses should not be used.

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PHYSIOLOGIC STANDARDIZATION

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., Feb. 26, 1910)

The Council has adopted the rule that it considers the phrase "physiologically standardized" or "assayed" as misleading, unless the standard and method are published in sufficient detail to permit of their control by independent investigators. The Council has further voted that this ruling and the reasons therefore, be published. In accordance with this order the following explanatory note is given.

W. A. PUCKNER, Secretary.

The chief credit for the practical introduction of "physiologic standardization" belongs to American pharmaceutical manufacturing houses, which deserve the highest commendation for voluntarily subjecting themselves to great expense and trouble in developing suitable methods of physiologic assay. Without wishing to detract from the credit which justly is due them, the Council nevertheless, feels constrained to call attention to the abuses to which the phrase "physiologically standardized" is liable. To the physician the phrase means that the preparations to which it is applied are made to conform to a definite standard. This obvious meaning, however, is entirely misleading, when it is remembered that each firm has its own standard and that that standard is kept secret, a practice which obtains almost universally. There is little if any more justification in calling such a preparation "standardized" than there would be in calling a diphtheria antitoxin "standardized" without stating its strength. The government would promptly proceed against the manufacturers of such an antitoxin. With the drugs, however, this would be more difficult, since there are no official methods of assay. Every manufacturer can therefore feel at liberty to employ any method of assay which suits his purpose or fancy. Indeed, he might even omit the performance of any test, without serious fear of discovery.

It is scarcely necessary to point out to what confusion and abuses this may lead. A dishonest or careless manufacturer may set himself a very low "standard." Another, more exacting, may set his standard many times as high—yet the products of both would, under the present loose meaning of the term, be called "physiologically standardized," and supposedly, therefore, be of uniform strength. The danger to the public is obvious.

The comparative experiments of Edmunds and Hale on "The Physiologic Standardization of Digitalis" demonstrate that the fear of want of uniformity, at least, is not ungrounded. Other investigations point in the same direction. The remedy for this condition lies in the establishment of official methods of assay; in their absence, however, a great deal would be accomplished if manufacturers who use the phrase "physiologically standardized" would define its exact meaning, so that their claims can be controlled, and

1. Abstracted in THE JOURNAL A. M. A., June 12, 1909, p. 1938.

their preparations compared with others for which the same claim is made. This is necessary for the protection of the public, and entails no serious sacrifice on the part of the manufacturers. The information which is demanded may once have been a valuable trade secret but it is so no longer since a choice of methods of physiologic assay is now available to any one who cares to look for the information.

In view of these facts, the Council believes that it should enter an emphatic protest against claims of "standardization" based on secret, widely fluctuating "standards;" and in the future it will not accept any preparation for which the claim of physiologic standardization is made unless the standard and method are published in sufficient detail to permit of their control by independent investigators.

CACTUS GRANDIFLORUS

Report of the Council on Pharmacy and Chemistry

(From *The Journal A. M. A.*, March 12, 1910)

The Council voted that *cactus grandiflorus* should not be accepted for New and Nonofficial Remedies, and that a statement be prepared for *THE JOURNAL* giving the reasons for this action. Accordingly the following report has been adopted by the Council and its publication authorized.

W. A. PUCKNER, Secretary.

CACTUS GRANDIFLORUS

The therapeutic value of this plant has been variously estimated by different observers. Experimental evidence as to its action is scanty and no complete chemical examination has ever been made.

Reputable men have testified that some of the plants of the cactus family contain very active principles, but so far experiments seem to prove that *cactus grandiflorus* has neither the action of *digitalis* nor that of *strychnin*. The principal contributions, clinical and experimental, for and against the drug, are set out below.

EXPERIMENTAL EVIDENCE

O. H. Myers¹ worked with a product which he calls *cactina* and which he regards as the active principle of the drug. (As no such substance as *cactina* is described in any materia

1. *New York Med. Jour.*, 1891, lili, 681-683

medica, it is impossible to state what Myers really used.) He found that it had a strychnin-like action and raised the blood pressure.

Hatcher comes to the conclusion: "Either Myers' work was a pure fabrication or he was dealing not with cactin but with a substance similar to the pellotin of Heffter, the action of which resembles that of strychnin to a certain extent."

E. Boinet and J. Boy-Teissier² experimented with an aqueous extract, an alcoholic extract, and with an alkaloid which they call "cactine." They concluded from three sets of experiments on frogs that extract of cactus produces, in ten minutes, a temporary increase in the heart's action which frequently repeated doses are required to maintain; and that large doses slow the heart and produce arrhythmia.

L. E. Sayre³ experimented with a preparation of cactus, made from the stem of the plant, by injecting it into the dorsal lymph space of the frog. There was seemingly an increase in the amplitude of the heart's action and an indication of a strengthened beat or increased force.

R. A. Hatcher⁴ states that it is possible that cactus grandiflorus, under certain conditions, may contain a principle with a strychnin-like action. But Hatcher made 10 experiments on frogs, 4 on cats, 6 on dogs, 2 on rabbits, and 1 on a guinea-pig, with Cactina pillets of the Sultan Drug Company and the cactin of the Abbott Alkaloidal Company. From 1 to 15 pillets in frogs and up to 25 in dogs were used at each dose. In no single instance was there any evidence of a digitalis-like or strychnin-like action, or, in fact, of any decided action of any kind whatever.

Gordon Sharp⁵ was unable to obtain either alkaloid or glucosid from the plant, but found a series of resins that caused contraction of the blood vessels of a frog. This was not a digitalis-like contraction, but depended, he believed, on simple acidity. On the heart of the frog the resins have little or no effect, comparisons being made with digitalis in the same animals. There is no proof that cactus grandiflorus itself shortens diastole, or in fact, that it has any special action on the heart muscle at all. Sharp experimented on himself with large doses of an extract made with alcohol 1 to 5, but got no noticeable results. He thinks that the plant may have some slight diuretic action.

2. Bull. Gen. de Therap., 1891, cxxi, 343-349.

3. Am. Pharm. Assn., 1906, liv, 405.

4. THE JOURNAL A. M. A., Sept. 21, 1907, pp. 1021-1024.

5. Practitioner, London, 1894, iii, 444-446.

Sayre submitted the preparation which he used in his experiments for more careful testing to E. M. Houghton, who reported that it had practically no action on the heart.

In commenting on Houghton's results, Reid Hunt said that they were confirmed by his own experiments. He did not deny, however, that the drug might have some therapeutic effect and that, in very large doses, it did affect the kidneys.

S. A. Mathews⁶ found one preparation of cactus (cactin—Abbott) absolutely inert so far as any effect on the heart is concerned. He found that cactina (Sultan Drug Co.) in very large doses depressed both the circulation and respiration. In this regard it differs from strychnin, and it has no resemblance to the action of digitalis, strophanthus or any of the heart stimulants. A dose of from 10 to 12 pillets administered intravenously to a 10 to 12 kg. dog exerted little or no influence on the heart or circulation; the larger dose may cause a slight fall in blood pressure. When 70 or more pillets were administered within two and a half hours the animal generally died.

The work of Boinet and Boy-Teissier also has been criticized by Hatcher on the ground that their most positive results were obtained with an alkaloid which no one at this day is able to prepare. The results quoted in this report, however, were obtained by the use of extracts of cactus so that it does not seem that they should be entirely rejected, whatever their value may be.

CLINICAL EVIDENCE

Clinical observations have been more abundant than exact, and a favorable action of the drug in some organic diseases of the heart has been reported; other observers would limit its use to functional arrhythmia, insisting that it is not a substitute for digitalis or aconite, but that it occupies a place distinct from either of those remedies.

P. W. Williams⁷ recommends cactus for functional heart disease, but, as a rule, found it useless in organic disease. He thinks it one of a class of remedies which act on the accelerator nerves and sympathetic ganglia, shortening the diastole and stimulating the spinal vasomotor nerve centers. Williams apparently relied on Myers for his knowledge of the pharmacologic action, and his paper is a fair example of the clinical studies of cactus.

6. THE JOURNAL A. M. A., March 21, 1908, 1, 956-958.

7. Practitioner, London, 1891, xlvii, 266-273.

Ellingwood⁸ claims that cactus is a cardiac tonic, acting on the accelerator nerves and heart ganglia, increasing muscular force and arterial tension. He recommends it in both organic and functional diseases.

Boinet and Boy-Teissier found that therapeutic doses of forty drops of tincture of cactus were without effect on the normal heart. In patients with noisy asystole (*asystolie bruyante*) the same dose produced no appreciable effect. In the period of latent non-compensation of true cardiac patients, from 80 to 100 drops a day increased the force of the failing heart. In patients with secondary heart disease with arrhythmia of nervous origin, daily doses of 80, 100 and 120 drops of the tincture were well tolerated for weeks; they seemed to increase the fulness of the pulse and regulated its rhythm. In spite of such large doses these observers never noticed any symptoms that could be attributed to a cumulative action. It must be remembered that the precise preparation of cactus which they used is not known.

Aulde⁹ recommends it as a cardiac tonic free from cumulative effects.

Gordon Sharp says: "The therapeutics of the subject, I think, are clear enough. Cactus grandiflorus cannot be included in our list of cardiac drugs. It is not even a simple stomachic tonic and at most all one can say is that it has small diuretic action."

Hatcher says: "Clinical testimony is so conflicting that between the extreme viws of Gordon Sharp and those of Ellingwood there is room for an honest difference of opinion concerning cactus grandiflorus."

Matthews himself took 100 granules of cactin (1/67 gr.—1 mg. each), 25 every four hours, without experiencing the least effect.

CONCLUSIONS

Reliable conclusions regarding the therapeutic use of cactus grandiflorus are rendered difficult on account of several factors.

1. It is uncertain what part of the plant contains the active principle if one exists; and its nature is unknown. The National Standard Dispensatory states that its "activity must be confined to the flower in some special stage of its development or to a certain part of it or to some parts gathered with it." This uncertainty may explain the negative results obtained by some observers but it makes the drug one that cannot be generally relied on and gives an excellent opportunity for the exploitation of proprietary preparations.

8. Med. Rec., New York, 1905, lxxvii, 857.

9. Practitioner, London, xlvii, 223; Therap. Gaz., 1890.

2. Some of the experimental work and much of the clinical evidence has been obtained and published under proprietary auspices. For this reason many of the therapeutic claims made for the drug must be viewed as merely the reflection of the exaggerated statements made by the advertisers of proprietary preparations.

3. The value of clinical evidence when unsupported by animal experimentation is much diminished by the tendency of enthusiastic and untrained observers to attribute to the drug given the effect really due to general remedial measures, psychic suggestion and so forth. While it must be admitted that valuable remedies may exist whose therapeutic properties cannot be revealed by animal experimentation, yet in the absence of such experimental evidence conclusions should be drawn with extreme caution.

Bearing these conditions in mind, the following statements seem to be justified: (a) The botanical, chemical and pharmaceutical properties of cactus are not sufficiently determined to make any available preparation a reliable remedy. (b) There is some evidence that cactus may be capable of affecting the animal heart and nervous system, but its action is not that ordinarily attributed to it. It does not increase the force of the heart beat. (c) While there is some clinical testimony as to its usefulness in functional diseases of the heart, the indications for its administration are at present too uncertain to afford a safe basis for recommending it.

4. While the drug may be deserving of further experimental and clinical investigation, this should be carried on in reliable pharmacologic laboratories and in clinics provided with facilities for exact observation.

PASSIFLORA AND DANIEL'S CONCENTRATED TINCTURE OF PASSIFLORA

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., March 19, 1910)

The Council has voted that the drug passiflora (passion flower) be not accepted for New and Nonofficial Remedies and has recommended that the following article be published in THE JOURNAL. It is considered important to call attention, not only to the lack of reliable evidence of the therapeutic value of passiflora, but also to the absurdity of the claims which are made for Daniel's concentrated tincture of passiflora, a preparation which has been already refused recognition.

W. A. PUCKNER, Secretary.

PASSIFLORA

Although passiflora was introduced into medicine nearly seventy years ago, the literature concerning it is not very extensive; it is not mentioned in the standard works on pharmacology and its chemistry seems never to have been worked out. There appears, also, to be no record of experimental investigations of the drug with reference to its pharmacologic action, except an article by I. Ott,¹ who used "Daniel's concentrated tincture." Ott claimed that it lessened the reflex irritability of the cord and paralyzed motion by acting on the motor centers in the cord, and that it increased the rate of respiration. He also stated that because of its action on the vasomotor centers it reduced the frequency of the heart-beat and lowered arterial tension, but these effects were only temporary.

On the clinical side the reports are not numerous and such as have been made do not appear to be based on very extensive trials nor on conditions of observation that would entitle them to more than slight consideration. S. D. Bullington² reports good results, but no cure, in one case of epilepsy, and improvement in a case of insomnia. W. J. Stapleton³ recommends it in the form of a concentrated tincture (not the one advertised so extensively), and states that he has used it with great success in insomnia, hysteria, neurasthenia, neuralgia, nervous and physical prostration, and in alcoholism. In his opinion its action is most apparent in cases of nervousness due to causes other than pain. S. Harnsberger⁴ reports two cases in which partial blindness followed the taking of potassium bromid and passion flower.

Extravagant and inconsistent claims are made for Daniel's concentrated tincture of passiflora in the advertising literature, where it is recommended for such a wide range of diseases as asthma, typhoid fever, convulsions and paralysis.

None of the evidence is sufficient to show that passiflora has therapeutic value; hence it is deemed inadvisable to include this drug in the list of nonofficial remedies.

CHINOSOL

Report of the Council on Pharmacy and Chemistry

(From *The Journal A. M. A.*, May 28, 1910)

Chinosol, a product for which the Parmele Pharmacal Company is the American agent, was the subject of a Council report which appeared in *THE JOURNAL*, Jan. 25, 1908. The company took exception to the findings in the report and

1. *Med. Bull.*, 1898, xx, 457-464.

2. *Nashville Jour. Med. and Surg.*, 1897, lxxxi, 107-109.

3. *Detroit Med. Jour.*, 1904-5, iv, 17.

4. *Virginia Med. Semimonthly*, 1898-9, iii, 392.

requested that Chinosol be reexamined. The request was granted, and the referee who made the first bacteriologic examination of the product—and who in this report will be called Referee I—reinvestigated Chinosol. An independent examination also was made by an expert (Referee II) who was not a member of the Council. The reports of Referees I and II were submitted to a third referee (Referee III), who in turn transmitted them to the Council. Copies of the reports of the referees were also sent to the Parmele Pharmacal Company, which objected to certain of the findings. The report of Referee III, based on the reply of the company, and on the findings of Referees I and II, appears below. The objections raised by the company to the second report were replied to by the Council, and with its reply were sent the results of the investigations made in Europe by Schneider and Seligman and by Charles J. Martin which confirmed the findings of the Council. After considering this further evidence, the company modified its claims and the Council accepted Chinosol for inclusion in New and Nonofficial Remedies.

W. A. PUCKNER, Secretary.

The Council on Pharmacy and Chemistry took up the consideration of Chinosol on its own initiative and published its report in *THE JOURNAL*, Jan. 25, 1908. The Parmele Pharmacal Co. requested a reconsideration of Chinosol on the ground that the preparation examined which bore the label of Franz Fritzsche & Co., Hamburg,¹ did not come from them, since it did not bear their label. The firm also submitted bacteriologic reports by Dr. W. H. Patterson and by the Lederle Laboratories of New York with findings that differed in certain important respects from those obtained by the investigation made at the instance of the Council, and expressed the desire to conform to the rules of the Council in the exploitation of the preparation. In its letter to the Council the Parmele Pharmacal Co. laid special stress on the report of the Lederle Laboratories, and stated that it felt confident "that your referee will find our tests confirmed in every instance and will not find confirmed his own tests, if he will use Chinosol bearing our label."

Assuming that there might be a difference in the two brands of Chinosol as claimed, and considering the fact that the company had been willing to alter, and had somewhat altered, its advertising matter, removing some of the objectionable features and had accepted to some extent the criticism of the

1. The Parmele Pharmacal Co. thought at the time the preparation used had been repacked by some American drug-house other than their own,* and did not intend to question the product of Franz Fritzsche & Co.

Council's first report, the Council granted reconsideration, and Chinosol was resubmitted to the original referee, who will be called Referee I in this report. Referee I having completed his reexamination of Chinosol,² the product at the request of the company and under revised rules of the Council, was submitted also to a new referee, not a member of the Council, who acted essentially in a professional advisory capacity to the Council, and who will be called Referee II in this report.³ The reports of both referees having been considered by the Council and preliminary action taken by it, the Parmele Pharmacal Co. was, in accordance with the rules of the Council, given an opportunity to examine the findings of the Council and the reports of its referees, and the company submitted statements in reply. These statements and the findings of its referees having been carefully considered, the Council reached the following conclusions in regard to the questions concerning Chinosol:

AN INTENSE ANTISEPTIC

In its first report the Council found that Chinosol "does possess considerable antiseptic action and that it is in this respect superior to carbolic acid. On this point the statements in the circulars³ are essentially correct." The findings of both our referees in the present investigation confirm this conclusion. As regards *Staphylococcus pyogenes aureus* and *Bacillus typhosus*, Chinosol is a better antiseptic than carbolic acid and equivalent to mercuric chlorid as an antiseptic. The findings of our first report and the claims of the Parmele Pharmacal Co. on this point are thus confirmed. [It should be stated that Chinosol as now marketed is free from 30 per cent. inert matter—potassium sulphate—and is, therefore, proportionately stronger than the brands examined by the Council's experts.]

A VERY POOR GERMICIDE

While there was no dispute concerning the antiseptic action of Chinosol, the findings of the Council in regard to its germicidal action disagreed fundamentally with the claims made for it in this respect by the Parmele Pharmacal Co. and with the findings of their experts. While the company had withdrawn its most extravagant claims concerning the germicidal power of Chinosol, it still claimed in the report of the Lederle Laboratories that Chinosol was superior to carbolic acid, and that in its action on *S. p. aureus* it was, in weak acid broth, "stronger than bichlorid" (not under other

2. The reports of Referees I and II and the protocols of Cooper and Martin appear on pages 52, 62 and 72, respectively.

3. The circulars of the Parmele Pharmacal Co.

conditions), and that in general Chinosol resembled more nearly the strength of bichlorid of mercury than it did that of carbolic acid. The three investigations made by our referees (two by Referee I and one by Referee II) lead to the definite conclusion that in aqueous as well as in acid broth Chinosol is much less effective as a germicide than is carbolic acid and vastly inferior to mercuric chlorid.⁴

[NOTE: The Parmele Pharmacal Company has now withdrawn its claim that Chinosol has superior germicidal power to either phenol (carbolic acid) or mercuric chlorid.]

DISTINCTION BETWEEN ANTISEPTIC AND GERMICIDE

The striking difference in these results from those reported by the Lederle Laboratories appears to be due essentially to the care taken by our experts to exclude the possibility of *antiseptic* action being mistaken for *germicidal* action (see the reports for details; the precaution consisted simply in inoculating *larger* volumes of culture medium in order to overcome by dilution the intense antiseptic powers of Chinosol). The validity of such precautions appears to be above question—the principle has been recognized and accepted by such authorities, for instance, as Martin and Chick, Riedel and Walker, and others in the field.

Martin and Cooper's Results:—A letter received from the Parmele Pharmacal Company was handed to Referee II for an opinion, inasmuch as the letter quoted the results of Chick and Martin and attempted to show that these favored the stand taken by the Parmele Pharmacal Co. It was seen at once that the results of Chick and Martin in no wise supported the views of the company, but lest any error be committed in interpretation, Referee II wrote to Professor Charles J. Martin, F. R. S., director of the Lister Institute of Preventive Medicine, London, asking for an expression of opinion of the results of his own and Dr. Chick's work in the light of the quotation of the Parmele Pharmacal Co. Professor Martin's attention was also drawn to the fact that in their experiments with Chinosol the *antiseptic action* had possibly been overlooked.

4. In their work on the germicidal power of corrosive sublimate, Chick and Martin (Jour. Hyg., 1908, viii, 654), in order to avoid the further action of mercury carried over in combination with the bacteria remove it with hydrogen sulphid. As such a subsequent exposure to hydrogen sulphid—which reduces the germicidal efficiency of bichlorid—would, except in the case of disinfection, possibly of fecal discharges, not occur in practice, this behavior does not affect the efficiency of corrosive sublimate as a practical disinfectant ("The value of corrosive sublimate as a practical disinfectant remains unassailed."—Chick). The hydrogen sulphid treatment was therefore not used by our referees. It is quite different with Chinosol, whose antiseptic action can be overcome by subsequent dilution—such as is quite possible or even probable in practice.

This letter was acknowledged and in a second letter Professor Martin wrote that Mr. A. E. Cooper, working with him, had repeated Referee II's observations on Chinosol and had confirmed the referee's results. Professor Martin expressed regret that he had omitted to ascertain in his first work (with H. Chick) whether Chinosol exhibited inhibition in such great dilution; a large number of organic disinfectants had been examined by them without their coming across this phenomenon. At the time too, they were not concerned with determining the germicidal value of Chinosol.

The following tables are an abridgement⁵ of the work and results of Mr. E. A. Cooper and Professor Martin:

SERIES I.

Organism used: *Staphylococcus pyogenes aureus*, broth culture 24 hours old. Several drops of this culture were deposited in the dilutions of phenol (carbolic acid) and Chinosol, and by means of a special pipette one drop containing 0.013 c.c. was carried over from each dilution to a tube containing 10 c.c. of broth and incubated.

APPARENT GERMICIDAL RESULTS WITH CHINOSOL

Agent.	Dilution Strength.	Time of Exposure in Disinfectant (Growth Results).		Ultimate Dilu- tion of Agent in 10 c.c. of Broth.
		15 Min.	30 Min.	
Phenol	7:1000	+	+	1:109,890
	9:1000	+	—	1: 85,470
	10:1000	—	—	1: 76,923
Chinosol . . .	80:1000	—	—	1: 9,615
	up to 200:1000	—	—	up to 1: 3,846

SERIES II

To eliminate the inhibitive or antiseptic action of Chinosol on *S. p. aureus*, one drop (0.013 c.c.) of the contents of the first broth tube was removed and deposited in a second one containing 10 c.c., and incubated.

GERMICIDAL ACTION ABSENT

Agent.	Dilution Strength.	Time of Exposure in Disinfectant (Growth Results).		Ultimate Dilu- tion of Agent in 10 c.c. of Broth.
		15 Min.	30 Min.	
Chinosol . . .	80:1000	+	+	1:7,396,150
	up to 200:1000	+	+	up to 1:3,958,460

Similarly using *Bacillus typhosus*, it was demonstrated that the antiseptic action of Chinosol was considerably less than on *S. p. aureus*, and germicidal action was absent.

It is, therefore, clear that what Chinosol could not effect on *S. p. aureus*, in strengths of 200:1000 parts, phenol (carbolic acid) accomplished in 10:1000 parts; this effectively demonstrates the superiority of phenol as a germicide over Chinosol.

5. The protocols of this work appear on page 72.

Schneider and Seligman's Work:—Of particular interest and importance in this connection is the work of Schneider and Seligman in the laboratory of Proskauer, *Institut für Infektionskrankheiten*, Berlin (*Ztschr. f. Hyg. u. Infektionskrankh.*, 58, 412-40). These investigators recognized clearly the importance of *avoiding the mistaking of antiseptic action for germicidal action* in the examination of disinfectants, and write as follows concerning Chinosol: "With Chinosol also, to which a disinfecting power equal to that of corrosive sublimate is ascribed, we obtained poor results by the 'thread method.' Whereas, for instance, only a 10 per cent. solution of Chinosol was able to kill within an hour the staphylococci dried on the threads, the ordinary method of transfer of the mixture of bacteria and disinfectant in the culture medium gave the false appearance of killing the bacteria in approximately the same time already in 1 per cent. to 2 per cent. solutions. That this last result is due only to antiseptic action (*Entwicklungshemmung*') need not be especially emphasized." Their results (*S. p. aureus* being used) are so characteristic of the question in dispute that they are reproduced here:

TABLE A

ANTISEPTIC ACTION NOT AVOIDED

Minutes	5	10	15	20	25	30
2 per cent.....	—	+	—	—	—	—
3 per cent.....	—	—	—	—	—	—

TABLE B

STAPHYLOCOCCI THREADS; ANTISEPTIC ACTION AVOIDED

Minutes	10	20	30	40	50	60
3 per cent.....	+	+	+	+	+	+
5 per cent.....	+	+	+	+	+	+
7 per cent.....	+	+	+	+	+	+
10 per cent.....	+	+	+	—	—	—

The results obtained in Table A were obtained without using the precaution to prevent antiseptic action; those obtained in Table B are the results found when the threads were washed with dilute alkali to remove adhering Chinosol before transferring them to nutrient media. In another set of experiments carbolic acid was used, also with *S. p. aureus*.

TABLE C

ANTISEPTIC ACTION NOT AVOIDED

Minutes	5	10	15	20	25	30
Phenol 1 per cent.....	+	+	+	+	+	+
Phenol 1.5 per cent....	+	—	—	—	—	—

TABLE D

THREADS WASHED WITH DILUTE ALKALI; ANTISEPTIC ACTION AVOIDED

Minutes	5	10	15	20	25	30
Phenol 2 per cent.....	—	—	—	—	—	—

The Council thus was obliged to confirm its original findings that while Chinosol is a powerful antiseptic, it is a very poor germicide, and the claims made for it in this respect must be rejected. It may be added that the Council has considered the question of physicians being given reliable information as to each of these properties a fundamental one.

ITS NON-POISONOUS CHARACTER

In the Council's first report the evidence of T. Weyl was quoted questioning the claim made that the use of Chinosol is free from the dangers of poisoning. Weyl's evidence and reliability having been questioned by the firm and experimental evidence by the Lederle Laboratories submitted contradicting his conclusions, the Council had some experiments bearing on this question carried out by its own expert.⁶ It finds that in so far as guinea-pigs and rabbits are concerned Chinosol is devoid of toxic power. The authority quoted in the first report is therefore found to be unreliable and Chinosol must be considered non-toxic.

CHEMICAL COMPOSITION OF CHINOSOL

In 1899 Rost-Sonntag showed (*Chem. Zentralbl.*, 1899, ii, 396, and *Arch. a. d. k. Gendhtsamte*, xv, 288-301), that Chinosol was a mixture. In its first report the Council confirmed the conclusions of Brahm, working in the physiologic institute of the University of Berlin, that Chinosol is not a sulphonate of oxyquinoline, as represented by the promoters of Chinosol, but a double salt or mixture of its sulphate with potassium sulphate. The result of these findings was accepted by the Parmele Pharmacal Co. and the correction made in its subsequent publications; the original error, according to the firm, was due to its accepting the statement of the U. S. Dispensatory, i. e., that Chinosol is an oxyquinoline sulphonate as authoritative in the matter. Chinosol is now no longer marketed as the double salt or mixture of oxyquinoline sulphate and potassium sulphate, but as pure normal (neutral) oxyquinoline sulphate $(C_9H_7NO)_2H_2SO_4$.⁷

ANTISEPTIC ACTION VS. GERMICIDAL ACTION

It seems of the greatest importance to the Council that antiseptic power be not mistaken for germicidal power and that physicians should be correctly informed as to these prop-

6. These appear in the report of Referee II; see page 71.

7. Zernik: *Apoth.-Ztg.*, 24, No. 63, p. 568.

erties of disinfectants⁸ recommended to them, so that they may decide for themselves in every given case which action they wish to produce. This seems especially important in the case of a substance, which, according to the findings in three expert examinations on the part of the Council, has very poor germicidal power, not at all comparable with that of bichlorid of mercury, as had been claimed by the Parmele Pharmacal Co. In view of this the Council ordered the publication of this report and refused to accept Chinosol for admission to "New and Nonofficial Remedies" until the claims made for its germicidal action had been modified in accordance with its findings.

[NOTE: The Parmele Pharmacal Company has re-submitted Chinosol with the advertising matter revised in accordance with the findings of the Council. All objectionable claims having been eliminated the Council reconsidered the product and accepted Chinosol for admission to New and Nonofficial Remedies.]

Report of Referee I

Of five samples of Chinosol, bearing the label of the Parmele Pharmacal Co., two were selected for the examination. One of these, marked "B," was purchased from a wholesale dealer, while the other, marked "C," was submitted by the Parmele Pharmacal Co.

In view of the lengthy and seemingly accurate report of the Lederle laboratories, and the special emphasis placed upon it by the Parmele Pharmacal Co., it was desirable to confirm or reject their findings irrespective of the previous results obtained by the referee with the Fritsche brand. Hence, tests were made to conform as closely as possible to the technic as described and used by the Lederle laboratories. Two essential points, however, had to be assumed by the referee. The first related to the size of the platinum loop employed in making the transfers. This is thrice given in the report as 500 millimeters—obviously a typographic error—which probably was intended to be 0.5 millimeter clear inside diameter; but of that there is no certainty. The second and equally important point concerned is the quantity of broth inoculated at each transfer. Regarding this the Lederle report is silent.

8. For example, in the disinfection of hands, instruments, linen or silk threads, etc., germicidal and not antiseptic power would be desired. Chinosol solution as dilute as 1:1000 had been recommended for these purposes. A glance at the tables, either of the referees or of Schneider and Seligman, will show the danger of assuming that complete disinfection is accomplished by such solutions in a reasonable length of time.

The influence of the size of the loop used and of the quantity of broth inoculated will be apparent from what follows. In the tests made by the referee the inoculations were made as indicated, into 5, 10 or even 50 c.c. of bouillon. The platinum wires were 0.5 and 0.2 mm. thick; the former having a loop 2 mm., the latter 0.5 mm. clear, internal diameter.

ANTISEPTIC ACTION

In the previous report the referee stated "that Chinosol does possess considerable antiseptic action and that in this respect it is superior to carbolic acid. On this point the statements in the circular (F. Fritsche's) are essentially correct." The Lederle report states that Chinosol is much stronger than carbolic acid in antiseptic power and at least the equal of bichlorid of mercury. It will be seen, therefore, that the referee's original report concedes the antiseptic action of Chinosol under the conditions of the tests and for the organisms employed. This is also corroborated by the second referee, as seen from his report.

It may be well to state that the limit of antiseptic power is a variable depending on a number of factors among which may be mentioned the number of cells transferred, the species of the organism employed and the vigor or physical condition of the strain used. Thus, the staphylococcus is inhibited by a considerably weaker Chinosol solution than is the typhoid bacillus. Moreover, a strain of the staphylococcus which has been weakened by exposure to an injurious agent, such as Chinosol or even impure distilled water, is inhibited by a concentration of Chinosol which itself would have no effect on the original vigorous strain. This fact has an important bearing in connection with the tests of the germicidal efficiency as will be shown.

Since there is essentially and has always been agreement regarding the antiseptic action of Chinosol, the real issue in dispute involves the claims made, then and now, for its germicidal power.

GERMICIDAL ACTION

The results of the previous tests of Chinosol were not in accord with the statements published in the Fritsche circular and they do not agree with the results brought forward in the report of the Lederle laboratories. The latter conclude their report with the statement that in water solutions Chinosol is much more powerful in its germicidal action than carbolic acid and that it resembles more nearly the strength of mercury bichlorid than it does that of carbolic acid.

The conclusions drawn above by the Lederle laboratories, in so far as mercuric chlorid is concerned, are not in accord with the results given in their own tables. Nor do they agree with their statement, on page 5 of the printed report, made in connection with tests 3-8 inclusive, that "Bichlorid in these tests was shown to be stronger than Chinosol."

This much can be readily seen on comparing their results, obtained with solutions of equal strengths (1:5,000) of Chinosol and bichlorid of mercury as tabulated below.

TABLE I
COMPARISON OF CHINOSOL AND MERCURY BICHLORID
(Compiled from the Report of the Lederle Laboratories)

	CHINOSOL, 1 to 5,000.	BICHLORID, 1 to 5,000.
Table 3 S. p. albus.	+ in 10 min. ; 0 in 20 min.	0 in 1 min.
Table 4 Typhoid bac.	+ in 90 min.	0 in 1 min.
Table 5 Anthrax bac.	+ in 90 min.	+ in 1 min. ; 0 in 5 min.
Table 6 S. p. aureus.	+ in 90 min.	+ in 1 min. ; 0 in 5 min.
Table 7 Typhoid bac.	+ in 90 min.	+ in 1 min. ; 0 in 5 min.
Table 8 Anthrax bac.	+ in 90 min.	+ in 30 min. ; 0 in 60 min.
Table 9 S. p. aureus.	+ in 10 min. ; 0 in 20 min.	+ in 90 min. ;
Table 10 Typhoid bac.	+ in 90 min.	0 in 1 min.
Table 11 Anthrax bac.	+ in 90 min.	+ in 10 min. ; 0 in 20 min.
Table 12 S. p. aureus.	+ in 90 min.	+ in 5 min. ; 0 in 10 min.
Table 13 Typhoid bac.	+ in 90 min.	0 in 1 min.
Table 14 Anthrax bac.	+ in 90 min.	+ in 30 min. ; 0 in 60 min.

In the above tabulation the sign + indicates growth and 0 its absence. It will be seen from the above that Chinosol, in a strength of 1 to 5,000, in 10 out of 12 tests does not destroy the test organism in 90 minutes, whereas mercury bichlorid in like strength, in 7 out of 12 trials in less than 5 minutes does destroy them. It may be remarked that No. 9 is the only test which shows an apparent superiority of Chinosol over bichlorid of mercury.

The comparative results obtained by the referee, shown in Tables II and III, accord with those of the Lederle laboratories as given above. Since, in like concentration, mercury bichlorid destroys the test organisms in about one minute while Chinosol fails to do this in ninety minutes it is clear that in like concentrations, Chinosol is *greatly inferior* to mercuric chlorid and any other claim must be considered as unwarranted.

CARBOLIC ACID

The conclusions of the Lederle laboratories with respect to carbolic acid are seemingly justified by the tests summarized in Tables 3 to 14 inclusive of their report. In seven out of the twelve tests the results decidedly favor their view that

Chinosol is much superior to carbolic acid. In the previous report of the referee it was held that Chinosol (Fritsche) was inferior to carbolic acid and hence this really is the only question at issue. It remains to be shown whether this divergence in conclusions is due to a difference in the two brands of Chinosol or to variation in technic.

According to the Lederle report a Chinosol solution of 1 to 100, in every test (Tables 3-14 inclusive), apparently destroys test organisms (*S. p. albus*, *S. p. aureus*, Typhoid bac., Anthrax bac.) within one minute since no growth was obtained. The same result was obtained (in tests 3-11 inclusive) with Chinosol solutions of 1 to 200, whereas in three tests (Nos. 12-14) a longer time was required. Even a Chinosol solution of 1 to 500 was apparently effective in less than one minute as seen from the results given in four out of the twelve tables (Nos. 3, 5, 6, 8), while a 1 to 1,000 solution in two tests (Nos. 5 and 6) killed in five and one minute, respectively.

By way of contrast it may be stated that the previous examination made by the referee gave, in some of the tests, results indicating that a Chinosol solution of 1 to 100 required more than sixty minutes to destroy the test organism.

It may be stated at this point that the results of the examination of the Parmele Chinosol are in agreement with those obtained with the Fritsche Chinosol. Hence, the explanation of this difference in results is to be sought in the technic employed. As already pointed out, Chinosol does possess intense antiseptic action *which must be effectually excluded if reliable results are desired*. Furthermore, it is necessary to take into consideration the fact that an organism once weakened through any cause is inhibited in its growth by the germicide in a concentration which would have no effect on the normal cell. Hence, while a Chinosol solution of 1 to 300,000 may inhibit the growth of a fairly vigorous strain of staphylococcus, one-tenth that amount may have the same action with an enfeebled organism. (Table V).

In the method employed by the Lederle laboratories, at the end of each time specified, two loops (not 500 mm. in diameter as given) were transferred from each tube of disinfectant to sterile broth medium in culture tubes. It was assumed that the slight amount of disinfectant thus carried over, was lost by the comparatively large quantity of broth with which it was mixed. In the absence of definite data as to the size of the loop used and the volume of broth inoculated it is not

possible to control their results as closely as might have been desired.

In the tests, the results of which are given in the following tables, 5 c.c. of an aqueous solution of the disinfectant was employed. This was freshly prepared without the aid of heat, for each experiment, by suitably diluting a 1 to 20 stock solution. Thus, 1 c.c. of this solution added to 4 c.c. of sterile distilled water gave the 1 to 100 solution.

The test organisms, grown on inclined agar for twenty-four hours, were taken up with sterile distilled water and, after filtration through a cotton-glass wool filter, the number of bacteria was determined by Wright's method and then adjusted so that each cubic centimeter contained 10,000 million bacteria. Fresh suspensions were made for each experiment, and these were kept in ice water until wanted. It is well to bear in mind that ordinary distilled water may have a marked injurious action which is favored by heat.

The solution of the disinfectant was inoculated with one loopful of the bacterial suspension. The size of the platinum loops employed have already been given. The transfers were made with a 2 mm. loop into 10 c.c. of bouillon, unless otherwise indicated.

The inoculated tubes were placed in an incubator for from four to six days, and when a growth occurred it was controlled by microscopic examination. The sign + indicates the presence of growth, while the sign — its absence.

TABLE II

ACTION OF DISINFECTANTS ON *STAPHYLOCOCCUS PYOGENES AUREUS**CHINOSOL "B"*

Dilution.	1:100	1:200	1:500	1:1,000	1:2,000	1:5,000
1 minute...	—	—	+	+	+	+
5 minutes..	—	+	+	+	+	+
10 minutes..	—	—	+	+	+	+
20 minutes..	—	—	—	+	+	+
30 minutes..	—	—	—	—	+	+
60 minutes..	—	—	—	—	+	+
90 minutes..	—	—	—	—	—	+

CHINOSOL "C"

Dilution.	1:100	1:200	1:500	1:1,000	1:2,000	1:5,000
1 minute...	—	—	+	+	+	+
5 minutes..	—	—	+	+	+	+
10 minutes..	—	—	—	+	+	+
20 minutes..	—	—	+	+	+	+
30 minutes..	—	—	—	+	+	+
60 minutes..	—	—	+	+	+	+
90 minutes..	—	—	—	—	+	+

CARBOLIC ACID

1 minute...	—	+	+	+	+
5 minutes..	—	+	+	+	+
10 minutes..	—	+	+	+	+
20 minutes..	—	+	+	+	+
30 minutes..	—	—	+	+	+
60 minutes..	—	—	—	+	+
90 minutes..	—	—	—	+	+

MERCURIC CHLORID

1 minute...	—	—	—	—	—
5 minutes..	—	—	—	—	—
10 minutes..	—	—	—	—	—
20 minutes..	—	—	—	—	—
30 minutes..	—	—	—	—	—
60 minutes..	—	—	—	—	—
90 minutes..	—	—	—	—	—

A survey of Table II will show at once the superiority of mercuric chlorid over Chinosol. It also *seems to show* that Chinosol is stronger than carbolic acid, but remembering that Chinosol has a greater antiseptic action than carbolic acid, it follows that the apparent germicidal action of Chinosol may be due to the Chinosol carried over by the 2 mm. loop used in making the transfers. That such is actually the case will be shown in Table IV and may be inferred from Table III.

A simple calculation, based on the quantity of liquid carried over with a 2 mm. loop into 10 c.c. of broth, will show that with a 1 to 100 solution it approximates 1 to 300,000 and with a 1 to 200 solution 1 to 600,000; an amount quite sufficient to inhibit the growth of a weakened staphylococcus.

TABLE III
ACTION OF DISINFECTANTS ON TYPHOID BACILLUS

CHINOSOL "B"

Dilution.	1:100	1:200	1:500	1:1,000	1:2,000	1:5,000
1 minute...	+	+	+	+	+	+
5 minutes..	+	+	+	+	+	+
10 minutes..	+	+	+	+	+	+
20 minutes..	—	—	+	+	+	+
30 minutes..	—	—	+	+	+	+
60 minutes..	—	—	—	+	+	+
90 minutes..	—	—	—	—	+	+

CHINOSOL "C"

1 minute...	+	+	+	+	+	+
5 minutes..	+	+	+	+	+	+
10 minutes..	+	+	+	+	+	+
20 minutes..	+	+	+	+	+	+
30 minutes..	+	+	+	+	+	+
60 minutes..	+	+	+	+	+	+
90 minutes..	—	+	+	+	+	+

CARBOLIC ACID

Dilution.	1:100	1:200	1:500	1:1,000	1:2,000	1:5,000
1 minute...	—	+	+	+	+	+
5 minutes..	—	+	+	+	+	+
10 minutes..	—	+	+	+	+	+
20 minutes..	—	+	+	+	+	+
30 minutes..	—	+	+	+	+	+
60 minutes..	—	—	+	+	+	+
90 minutes..	—	—	+	+	+	+

MERCURIC CHLORID

1 minute...	—	—	—	—	—	—
5 minutes..	—	—	—	—	—	—
10 minutes..	—	—	—	—	—	—
20 minutes..	—	—	—	—	—	—
30 minutes..	—	—	—	—	—	—
60 minutes..	—	—	—	—	—	—
90 minutes..	—	—	—	—	—	—

Since the antiseptic value of Chinosol with reference to the typhoid bacillus is much less than that for *Staphylococcus pyogenes aureus* it follows that the inhibitive action, in the sub-cultures, is considerably less than as shown in Table II, and hence, the germicidal results given in this table are more nearly correct. It will be seen from this experiment that carbolic acid (1 to 100) is more effective than either sample of Chinosol; and that mercuric chlorid again shows a considerably greater germicidal value.

EFFECT OF SIZE OF LOOP USED FOR INOCULATION

The results given in Table II indicate the probability that Chinosol in a concentration of 1 to 100 failed to give growth, not because of a germicidal action, but rather on account of its antiseptic action. To test the matter still further, the experiment given in Table IV was carried out. Aqueous suspensions of the test bacteria were prepared as before; likewise, an aqueous solution of Chinosol "C" (1 to 100) was prepared. Portions of 5 c.c. of this solution were placed in four tubes, two of which were inoculated with *S. p. aureus* and two with the typhoid bacillus. The inoculations were made with one loopful of the bacterial suspension, using a 2 mm. and 0.5 mm. loop respectively. The former carried over at least fifty times as many bacteria as the latter into the disinfecting solution. The transfers (one loopful) were made at the time given, in duplicate, using, however, a 2 mm. loop for one set of inoculations and a 0.5 mm. one for the other. The tubes inoculated contained 10 c.c. of broth. The smaller loop, consequently carried over a lesser number of organism, and, what was more important, less of the antiseptic agent.

TABLE IV

ACTION OF CHINOSOL "C," 1 TO 100

5 c.c. Solution Inoculated with 1 Loop.		2 mm. diam.		0.5 mm. diam.	
To 10 c.c. Broth Trans- ferred 1 Loop.		2 mm.	0.5 mm.	2 mm.	0.5 mm.
<i>STAPHYLOCOCCUS PYOGENES AUREUS</i>					
1 minute.....	—	+	—	—	+
5 minutes.....	—	+	—	—	+
10 minutes.....	—	+	—	—	+
20 minutes.....	—	+	—	—	—
30 minutes.....	—	—	—	—	—
60 minutes.....	—	—	—	—	—
90 minutes.....	—	—	—	—	—
<i>TYPHOID BACILLUS</i>					
1 minute.....	+	+	+	+	+
5 minutes.....	+	+	+	+	+
10 minutes.....	+	+	+	+	+
20 minutes.....	+	+	+	+	+
30 minutes.....	+	+	+	+	+
60 minutes.....	+	+	—	—	—
90 minutes.....	—	+	—	—	—

This table shows clearly that Chinisol, in a strength of 1 to 100, does not kill the test organisms as would seem to be indicated in Tables II and III or in those of the Lederle report. In the case of *S. p. aureus*, when a 2 mm. loop is used to inoculate the disinfectant and to make the transfers (first column) to broth, no growth was obtained just as in Table II, but this failure of the organism to develop was not due to its destruction since the transfers with a 0.5 mm. loop (second column) gave a growth as late as twenty minutes. Similarly, the transfers with a 2 mm. loop from the tube inoculated with a smaller number of organisms (one 0.5 mm. loop) gave no growth, while those made with the 0.5 mm. loop were positive up to ten minutes.

As pointed out under Table II, the amount of disinfectant carried over from a 1 to 100 solution by a 2 mm. loop into 10 c.c. of broth approximates 1 to 300,000. This concentration is sufficient to inhibit the growth of a weakened staphylococcus, but has only a slight effect on the typhoid bacillus. Hence, in the case of the latter, the inoculations with a 2 mm. loop do not differ materially from those with a 0.5 mm. loop. The 2 mm. loop transfers agree with the results given under Table III, and it is evident that the failure to grow at ninety minutes is here also due to the antiseptic carried over.

COMPARISON OF CHINOSOL AND CARBOLIC ACID

In this experiment two tubes, containing 5 c.c. of the respective disinfectants, were each inoculated with one loopful of the standard staphylococcus suspension, using a 2 mm. loop; two other tubes were similarly inoculated with the 0.5 mm. loop. The transfers were made with the 0.5 mm. loop, as indicated in the table, into 5 and 10 c.c. of broth, respectively.

TABLE V

5 C.C. DISINFECTANT (1 TO 100) PLUS *S. P. AUREUS*

Solution Inoculated with 1 Loop.		2 mm. diam.		0.5 mm. diam.	
No. of 0.5 mm. Loops	Transferred to Broth.	2 into 5 c.c.	1 into 10 c.c.	2 into 5 c.c.	1 into 10 c.c.
<i>CHINOSOL "C"</i>					
1 minute.....		+	+	+	+
5 minutes.....		+	+	+	+
10 minutes.....		+	+	+	+
20 minutes.....		+	+	+	+
30 minutes.....		—	+	—	—
60 minutes.....		—	—	—	—
90 minutes.....		—	—	—	—
<i>CARBOLIC ACID</i>					
1 minute.....		+	+	—	—
5 minutes.....		—	—	—	—
10 minutes.....		—	—	—	—
20 minutes.....		—	—	—	—
30 minutes.....		—	—	—	—
60 minutes.....		—	—	—	—
90 minutes.....		—	—	—	—

TABLE VI

5 C.C. DISINFECTANT (1:100) PLUS *TYPHOID BACILLUS*

Solution Inoculated with 1 Loop.		2 mm. diam.		0.5 mm. diam.	
No. of 0.5 mm. Loops	Transferred to Broth.	2 into 5 c.c.	1 into 10 c.c.	2 into 5 c.c.	1 into 10 c.c.
<i>CHINOSOL "C"</i>					
1 minute.....		+	+	+	+
5 minutes.....		+	+	+	+
10 minutes.....		+	—	—	—
20 minutes.....		+	+	—	—
30 minutes.....		—	—	—	—
60 minutes.....		—	—	—	—
90 minutes.....		—	—	—	—
<i>CARBOLIC ACID</i>					
1 minute.....		—	—	—	—
5 minutes.....		—	—	—	—
10 minutes.....		—	—	—	—
20 minutes.....		—	—	—	—
30 minutes.....		—	—	—	—
60 minutes.....		—	—	—	—
90 minutes.....		—	—	—	—

An examination of Tables V and VI, as well as of Tables II and III, will show that carbolic acid, in a concentration of 1 to 100, kills the test objects, *S. p. aureus* and typhoid bacillus, usually in less than one minute. The only exception is shown in the first two columns of Table V, where, however, the germicidal action was complete in five minutes. These results with carbolic acid are confirmatory of those given in the Lederle report (8 tests), but on the other hand their results with Chinosol are wholly at variance with those given in the above tables.

It will be seen further, from Tables V and VI, that carbolic acid, instead of being inferior to Chinosol, is in reality, under the conditions of experiment as here given, superior to the latter as a *germicide*.

While the Lederle report seems to indicate that Chinosol is superior to carbolic acid, since it apparently destroyed the test objects in less than one minute when solutions of 1 to 100 and 1 to 200 were employed, while 1 to 500 and 1 to 1,000 gave at times equally marked results, these tests of the referee show quite the reverse, the inferiority of Chinosol as compared with carbolic acid.

In all the experiments given above, aqueous solutions of the disinfectants were employed. Some tests were also made, with serum and defibrinated blood, which were even more unfavorable to Chinosol. The addition of 1 c.c. of 1 to 20 Chinosol to 4 c.c. of serum or blood does not give a 1 to 100 solution, as might be expected, owing to the formation of a heavy crystalline precipitate. *Because of this precipitation the germicidal action of Chinosol is lessened and all but destroyed.* Thus, in one test, the Chinosol blood mixture (1 to 100) inoculated with a 2 mm. loop of a suspension of *S. p. aureus* (10,000 million per cubic centimeter) gave a positive growth at the end of *eighteen hours*; whereas a similar carbolic acid-blood mixture failed to give growths after thirty minutes.

To sum up, the examination of Chinosol bearing the label of Parmele Pharmacal Co. (and manufactured by Fritsche) yields essentially the same results as those previously obtained with a specimen of Chinosol bearing the label of F. Fritsche & Co. The findings of the referee show that as regards *S. p. aureus* and *B. typhosus*, Chinosol is a better antiseptic than phenol and the equivalent of bichlorid of mercury in antiseptic action, but quite inferior to phenol and vastly inferior to mercuric chlorid as a *germicide*.

CLAIMS MADE

The following claims of the firm are given as instances which, partly on account of their ambiguity of language and liability to be misleading, partly on account of their exaggerated character when viewed in the light of our findings, are considered thoroughly objectionable and in need of correction in content and in phraseology.

"More Prompt and Efficient than Carbolic Acid, Corrosive Sublimate, Formalin, Creolin, Saprol, or any other antiseptic and germicide which can be safely applied in and on the human body."

"Experiments on animals with even weak solutions of Chinosol have shown that the virulence of pathogenic germs and the toxins present was promptly arrested. Where proper strength solutions of Chinosol were used, the germs were promptly killed."

"The value of Chinosol as a bactericide is thus proved beyond question when it is stated that it will—in a solution of 1 to 1,000—kill the bacilli of anthrax in a very few minutes."

The context to this last quotation might lead one to infer that this refers to the animal or subject, but it probably has to do with a test-tube experiment. If so, the Lederle report offers but little to support the statement. Thus, while in Table V of their report the 1 to 1,000 Chinosol apparently kills the anthrax bacillus in five minutes, in Table VIII it requires ninety minutes to accomplish a like result. In Table XI more than ninety minutes is required; while a 1 to 500 solution requires ninety minutes apparently to kill. In Table XIV Chinosol in strengths of 1 to 1,000, 1 to 500 and even 1 to 200 requires ninety minutes. In other words, this very broad statement, based on some isolated tests, does not take into consideration the facts as a whole.

[NOTE.—Since the above was written the advertising matter of the firm has been thoroughly revised, the claims objected to have been eliminated and Chinosol has been accepted for admission to New and Nonofficial Remedies.]

Report of Referee II

Two samples of Chinosol in original packages were received for examination, marked respectively, "A" and "D." Sample "A," an original unbroken package, bearing the label of the Parmele Pharmacal Company, the substance in powder form, alone was used for the tests.

TECHNIC

In the main, the technic of the Lederle laboratories was followed. Departures were made in several instances, namely, in regard to the size of the platinum loop, which was of Brown and Sharpe gauge No. 22 and was 2 mm. in inside

diameter; the bacterial suspensions were always made up fresh in distilled water, in the manner described below; and used at once, and for the antiseptic tests the solutions of reagents were made not in distilled water but in 0.5 per cent. acid broth, and all broths were made from beef, not from veal. Transfers were always made to 50 c.c. of nutrient broth.

Antiseptic Tests.—The solutions of reagents were made up in beef broth of a reaction 0.5 per cent. acid to phenolphthalein; the carbolic acid used was in the crystalline form.

Bacterial Cultures Used.—Two strains of *Staphylococcus pyogenes aureus*, recently isolated from two individual cases of suppuration, and two laboratory stock cultures of *Bacillus typhosus* were used for the tests. In regard to the latter two organisms, it may be said that before using for the tests they were rejuvenated according to the method of Fuller and Johnson. For each experiment the respective cultures were grown on slanted agar for twenty-four hours at 37 C. Suspensions from these were made by pouring 5 c.c. of sterile distilled water on the agar slant, the bacteria then scraped from the slanted surface of the agar with a loop and thoroughly shaken to dissolve clumps, and finally, to make each suspension more uniform, it was filtered through sterile absorbent cotton. One loopful of each suspension was used for the inoculations into the various antiseptic solutions, and from each of these solutions one loopful of the contents was transferred to 50 c.c. of nutrient beef broth.

Incubation.—The incubation was carried out at 37 C. throughout the experiments. The period of incubation was in all cases four days, and at the end of that time each tube showing the least suspicion of or any degree of cloudiness was examined both by the microscope and by subculture on agar slants.

Germicidal Tests.—The solutions of the several reagents were made up according to the method of the Lederle laboratories; that of carbolic acid was made from crystals.

The bacterial suspensions were prepared as detailed in the foregoing; and one loopful of the bacterial suspension was transferred to each of the germicidal solutions, and, after a lapse of 1, 5, 10, 20, 30, 60 and 90 minutes, transfers of one loopful from each tube were made into 50 c.c. of beef broth and incubated for four days at 37 C., and all cloudy tubes were examined both microscopically and culturally.

In the matter of making up bacterial suspensions, it was found by preliminary tests that there was no difference in re-

sults obtained by making the suspension by Wright's method and by the method described as used in these series of experiments; thus an unnecessary expenditure of both time and labor was saved. In making the antiseptic tests, it was considered a fairer test, approximating nearer to the requirements of practice, to have the several reagents dissolved in 0.5 per cent. acid broth than in distilled water, as was done by the Lederle laboratories.

The checking up of all tubes, showing any degree of cloudiness, by both microscopic and cultural examination, practically ruled out all chance of error arising by possible contamination of the tubes by foreign micro-organisms.

In carrying out the germicidal tests, by transferring one loopful of the contents of the mixture in the reagent solutions to so large a quantity as 50 c.c. of broth, errors due to the result of antiseptic action in the culture medium were to all intents and purposes excluded. Table XI shows how, in the employment of relatively small quantities of nutrient fluids, antiseptic action may be mistaken for germicidal action, and wholly erroneous conclusions drawn.

TABLE VII
ANTISEPTIC TESTS: DILUTIONS IN 0.5 PER CENT. ACID BROTH

Dilution.	1:5000.	1:10000.	1:20000.	1:50000.	1:100000.	1:200000.	1:300000.	1:500000.	1:1000000.
<i>CHINOSOL "A"</i>									
S. p. aureus I...	—	—	+	+	+	++	++	++	++
S. p. aureus VI..	—	—	—	+	+	++	++	++	++
B. typhos. "Y"...	—	—	—	+	+	++	++	++	++
B. typhos. "X" ..	—	—	+	+	+	++	++	++	++
<i>CARBOLIC ACID</i>									
S. p. aureus I...	+	++	++	++	++	++	++	++	++
S. p. aureus VI..	+	++	++	++	++	++	++	++	++
B. typhos. "Y"...	+	++	++	++	++	++	++	++	++
B. typhos. "X" ..	+	++	++	++	++	++	++	++	++
<i>MERCURIC CHLORID</i>									
S. p. aureus I...	—	—	—	+	+	++	++	++	++
S. p. aureus VI..	—	—	+	+	+	++	++	++	++
B. typhos. "Y"...	—	—	+	+	+	++	++	++	++
B. typhos. "X" ..	—	—	—	+	+	++	++	++	++

The + sign everywhere signifies slight cloudiness due to proven growth; the ++ indicates well-marked cloudiness; while the minus sign denotes absence of any cloudiness. Chinosol gave precipitates in dilutions of 1 to 5,000, 1 to 10,000 and 1 to 50,000. Bichlorid of mercury did likewise. In all cases where the cloudiness was very slight, subcultures were made on agar, and microscopic examination was made of the fluid itself.

TABLE VIII

GERMICIDAL TESTS: DILUTION OF GERMICIDES IN STERILE
DISTILLED WATER

Dilution of: 1:100 1:200 1:500 1:1,000 1:5,000

CHINOSOL "A" WITH S. P. AUREUS I

1 minute....	+	+	+	+	+
5 minutes....	—	+	+	+	+
10 minutes....	—	+	+	+	+
20 minutes....	—	+	+	+	+
30 minutes....	—	+	+	+	+
60 minutes....	—	+	+	+	+
90 minutes....	—	—	+	+	+

CHINOSOL "A" WITH S. P. AUREUS VI

1 minute....	+	+	+	+	+
5 minutes....	+	+	+	+	+
10 minutes....	+	+	+	+	+
20 minutes....	—	+	+	+	+
30 minutes....	—	+	+	+	+
60 minutes....	—	+	+	+	+
90 minutes....	—	—	+	+	+

Dilution of: 1:100 1:200 1:500 1:1,000 1:1,500

CHINOSOL "A" WITH B. TYPHOS. "Y."

1 minute....	+	+	+	+	+
5 minutes....	+	+	+	+	+
10 minutes....	+	+	+	+	+
20 minutes....	+	+	+	+	+
30 minutes....	+	+	+	+	+
60 minutes....	+	+	+	+	+
90 minutes....	—	+	+	+	+

CHINOSOL "A" WITH B. TYPHOS. "X."

1 minute....	+	+	+	+	+
5 minutes....	+	+	+	+	+
10 minutes....	+	+	+	+	+
20 minutes....	+	+	+	+	+
30 minutes....	+	+	+	+	+
60 minutes....	+	+	+	+	+
90 minutes....	+	+	+	+	+

CARBOLIC ACID WITH S. P. AUREUS I

1 minute....	+	+	+	+	+
5 minutes....	—	+	+	+	+
10 minutes....	—	+	+	+	+
20 minutes....	—	+	+	+	+
30 minutes....	—	—	+	+	+
60 minutes....	—	—	+	+	+
90 minutes....	—	—	—	+	+

CARBOLIC ACID WITH S. P. AUREUS VI

1 minute.....	+	+	+	+	+
5 minutes.....	+	+	+	+	+
10 minutes.....	—	+	+	+	+
20 minutes.....	—	+	+	+	+
30 minutes.....	—	+	+	+	+
60 minutes.....	—	+	+	+	+
90 minutes.....	—	—	+	+	+

CARBOLIC ACID WITH B. TYPHOS. "Y."

1 minute.....	+	+	+	+	+
5 minutes.....	—	+	+	+	+
10 minutes.....	—	+	+	+	+
20 minutes.....	—	+	+	+	+
30 minutes.....	—	+	+	+	+
60 minutes.....	—	—	+	+	+
90 minutes.....	—	—	+	+	+

CARBOLIC ACID WITH B. TYPHOS. "X."

1 minute.....	+	+	+	+	+
5 minutes.....	—	+	+	+	+
10 minutes.....	—	+	+	+	+
20 minutes.....	—	+	+	+	+
30 minutes.....	—	+	+	+	+
60 minutes.....	—	+	+	+	+
90 minutes.....	—	—	+	+	+

MERCURIC CHLORID WITH S. P. AUREUS I

1 minute.....	—	—	—	—	—
5 minutes.....	—	—	—	—	—
10 minutes.....	—	—	—	—	—
20 minutes.....	—	—	—	—	—
30 minutes.....	—	—	—	—	—
60 minutes.....	—	—	—	—	—
90 minutes.....	—	—	—	—	—

MERCURIC CHLORID WITH S. P. AUREUS VI

1 minute.....	—	—	—	—	—
5 minutes.....	—	—	—	—	—
10 minutes.....	—	—	—	—	—
20 minutes.....	—	—	—	—	—
30 minutes.....	—	—	—	—	—
60 minutes.....	—	—	—	—	—
90 minutes.....	—	—	—	—	—

Dilution of: 1:100 1:200 1:500 1:1,000 1:5,000

MERCURIC CHLORID WITH B. TYPHOS. "Y."

1 minute.....	—	—	—	—	—
5 minutes.....	—	—	—	—	—
10 minutes.....	—	—	—	—	—
20 minutes.....	—	—	—	—	—
30 minutes.....	—	—	—	—	—
60 minutes.....	—	—	—	—	—
90 minutes.....	—	—	—	—	—

MERCURIC CHLORID WITH B. TYPHOS. "X."

1 minute.....	—	—	—	—	—
5 minutes.....	—	—	—	—	—
10 minutes.....	—	—	—	—	—
20 minutes.....	—	—	—	—	—
30 minutes.....	—	—	—	—	—
60 minutes.....	—	—	—	—	—
90 minutes.....	—	—	—	—	—

TABLE IX

GERMICIDAL TESTS: DILUTIONS OF GERMICIDES IN STERILE 0.5 PER CENT. ACID BROTH

Dilution of: 1:100 1:200 1:500 1:1,000 1:1,500

CHINOSOL "A" WITH S. P. AUREUS VI

1 minute.....	+	+	+	+	+
5 minutes....	+	+	+	+	+
10 minutes....	+	+	+	+	+
20 minutes....	+	+	+	+	+
30 minutes....	+	+	+	+	+
60 minutes....	+	+	+	+	+
90 minutes....	+	+	+	+	+

CHINOSOL "A" WITH B. TYPHOS. "Y"

1 minute.....	+	+	+	+	+
5 minutes....	+	+	+	+	+
10 minutes....	+	+	+	+	+
20 minutes....	+	+	+	+	+
30 minutes....	+	+	+	+	+
60 minutes....	+	+	+	+	+
90 minutes....	+	+	+	+	+

CARBOLIC ACID WITH S. P. AUREUS VI

1 minute.....	+	+	+	+	+
5 minutes....	+	+	+	+	+
10 minutes....	—	+	+	+	+
20 minutes....	—	+	+	+	+
30 minutes....	—	+	+	+	+
60 minutes....	—	+	+	+	+
90 minutes....	—	+	+	+	+

CARBOLIC ACID WITH B. TYPHOS. "Y"

1 minute.....	+	+	+	+	+
5 minutes....	+	+	+	+	+
10 minutes....	+	+	+	+	+
20 minutes....	—	+	+	+	+
30 minutes....	—	+	+	+	+
60 minutes....	—	+	+	+	+
90 minutes....	—	+	+	+	+

MERCURIC CHLORID WITH S. P. AUREUS VI

1 minute.....	—	—	—	—	+
5 minutes....	—	—	—	—	+
10 minutes....	—	—	—	—	+
20 minutes....	—	—	—	—	—
30 minutes....	—	—	—	—	—
60 minutes....	—	—	—	—	—
90 minutes....	—	—	—	—	—

Dilution of: 1:100 1:200 1:500 1:1,000 1:1,500

MERCURIC CHLORID WITH B. TYPHOS. "Y"

1 minute.....	—	—	—	+	+
5 minutes....	—	—	—	—	+
10 minutes....	—	—	—	—	—
20 minutes....	—	—	—	—	—
30 minutes....	—	—	—	—	—
60 minutes....	—	—	—	—	—
90 minutes....	—	—	—	—	—

Chinosol gives a heavy precipitate in dilutions of 1 to 100, 1 to 200, and very slight precipitate in 1 to 500, 1 to 1,000 and 1 to 5,000.

Carbolic acid gives a slight precipitate in dilutions of 1 to 100 and 1 to 200.

Mercuric chlorid gives a heavy precipitate in dilutions of 1 to 100, 1 to 200, 1 to 500, 1 to 1,000, and a moderate precipitate in 1 to 5,000.

TABLE X

GERMICIDAL TESTS: DILUTIONS OF THE GERMICIDES IN 3 PER CENT. ACID BROTH

Dilution of: 1:100 1:200 1:500 1:1,000 1:5,000

CHINOSOL "A" WITH S. P. AUREUS VI

1 minute....	+	+	+	+	+
5 minutes....	+	+	+	+	+
10 minutes....	+	+	+	+	+
20 minutes....	+	+	+	+	+
30 minutes....	+	+	+	+	+
60 minutes....	+	+	+	+	+
90 minutes....	+	+	+	+	+

CHINOSOL "A" WITH B. TYPHOS. "Y"

1 minute....	+	+	+	+	+
5 minutes....	+	+	+	+	+
10 minutes....	+	+	+	+	+
20 minutes....	+	+	+	+	+
30 minutes....	+	+	+	+	+
60 minutes....	+	+	+	+	+
90 minutes....	+	+	+	+	+

CARBOLIC ACID WITH S. P. AUREUS VI

1 minute....	—	+	+	+	+
5 minutes....	—	+	+	+	+
10 minutes....	—	+	+	+	+
20 minutes....	—	+	+	+	+
30 minutes....	—	+	+	+	+
60 minutes....	—	+	+	+	+
90 minutes....	—	+	+	+	+

CARBOLIC ACID WITH B. TYPHOS. "Y"

1 minute....	—	+	+	+	+
5 minutes....	—	+	+	+	+
10 minutes....	—	+	+	+	+
20 minutes....	—	+	+	+	+
30 minutes....	—	+	+	+	+
60 minutes....	—	+	+	+	+
90 minutes....	—	+	+	+	+

MERCURIC CHLORID WITH S. P. AUREUS VI

1 minute....	—	—	—	—	+
5 minutes....	—	—	—	—	+
10 minutes....	—	—	—	—	—
20 minutes....	—	—	—	—	—
30 minutes....	—	—	—	—	—
60 minutes....	—	—	—	—	—
90 minutes....	—	—	—	—	—

Dilution of:	1:100	1:200	1:500	1:1,000	1:5,000
MERCURIC CHLORID WITH <i>B. TYPHOS.</i> "Y"					
1 minute.....	+	+	+	+	+
5 minutes....	—	—	—	+	+
10 minutes....	—	—	—	—	+
20 minutes....	—	—	—	—	+
30 minutes....	—	—	—	—	—
60 minutes....	—	—	—	—	—
90 minutes....	—	—	—	—	—

Chinosol forms no precipitate in any dilution.

Carbolic acid forms a slight precipitate in dilutions of 1 to 100 and 1 to 200.

Mercuric chlorid forms a heavy precipitate in all dilutions up to 1 to 1,000, and a less heavy precipitate in 1 to 5,000.

In the following experiments (Table XI) a "loopful" of each mixture containing the bacteria and the concentration of *Chinosol* indicated, was transferred to 5 c.c., to 10 c.c. and to 50 c.c. broth in order to determine whether the negative results obtained in the transfer to the smaller volumes were due to the actual *killing* of the bacteria by the disinfectant or whether the negative results of the transfer to *smaller* volumes were not due rather to the antiseptic action of the *Chinosol* carried over in the "loopful" into the broth, which would be diminished simply by dilution in larger volumes of broth.

TABLE XI

ANTISEPTIC ACTION OF CHINOSOL IN GERMICIDAL TESTS IN STERILE DISTILLED WATER

Dilution of:	1:100	1:200	1:500	1:1,000	1:5,000
<i>B. TYPHOS.</i> "Y" IN 5 C.C. BROTH					
1 minute.....	—	—	+	+	+
5 minutes....	—	—	+	+	+
10 minutes....	—	—	+	+	+
20 minutes....	—	—	+	+	+
30 minutes....	—	—	+	+	+
<i>B. TYPHOS.</i> "Y" IN 10 C.C. BROTH					
1 minute.....	—	+	+	+	+
5 minutes....	—	+	+	+	+
10 minutes....	—	+	+	+	+
20 minutes....	—	+	+	+	+
30 minutes....	—	+	+	+	+
<i>B. TYPHOS.</i> "Y" IN 50 C.C. BROTH					
1 minute.....	+	+	+	+	+
5 minutes....	+	+	+	+	+
10 minutes....	+	+	+	+	+
20 minutes....	+	+	+	+	+
30 minutes....	+	+	+	+	+

Dilution of: 1:100 1:200 1:500 1:1,000 1:5,000

S. P. AUREUS "II" IN 5 C.C. BROTH

1 minute.....	—	—	—	+	+
5 minutes.....	—	—	—	—	+
10 minutes.....	—	—	—	—	+
20 minutes.....	—	—	—	—	+
30 minutes.....	—	—	—	—	+

S. P. AUREUS "II" IN 10 C.C. BROTH

1 minute.....	—	—	—	—	+
5 minutes.....	—	—	—	—	+
10 minutes.....	—	—	—	—	+
20 minutes.....	—	—	—	—	+
30 minutes.....	—	—	—	—	+

S. P. AUREUS "II" IN 50 C.C. BROTH⁹

1 minute.....	+	+	+	+	+
5 minutes.....	+	+	+	+	+
10 minutes.....	—	+	+	+	+
20 minutes.....	—	+	+	+	+
30 minutes.....	—	+	+	+	+

The above results prove that the apparent germicidal activity of the Chinosol, when the transfers are made to relatively small amounts of broth, is actually antiseptic, and is more marked in the less resistant staphylococcus.

EFFECTS OF CHINOSOL ON ANIMALS

To ascertain whether Chinosol has poisonous qualities some of the material was fed and injected into animals as detailed in the following experiments:

CONCLUSIONS

In the light of the results obtained in these series of experiments, it seems fair to conclude that:

1. As regards *S. p. aureus* and *B. typhosus*, Chinosol is a better *antiseptic* than carbolic acid and equivalent to mercuric chlorid.

2. In watery solution, Chinosol, so far as *S. p. aureus* and *B. typhosus* are concerned, is somewhat inferior to carbolic acid as a *germicide*, and vastly inferior to mercuric chlorid.

3. In 0.5 per cent. acid broth, and particularly so in 3.0 per cent. acid broth, Chinosol, so far as *S. p. aureus* and *B. typhosus* are concerned, is as a *germicide* much less effective than carbolic acid, and not to be compared in activity to mercuric chlorid.

4. In so far as guineapigs and rabbits are concerned, it is clear that Chinosol, under the conditions of the experiments, unless given in enormous doses, is practically devoid of toxic power.

9. This test was repeated independently by a second person, and the same result was obtained.

No.	Date.	Animal.	Weight.	Chinosol.	How Given.	Result.
1	February 25.....	Guinea-pig	450 gm.	3 gm. powder	Stomach tube	} Inactive; suffered discomfort; diarrhea
	February 26.....	Guinea-pig	450 gm.	5 tablets ¹⁰	Mixed with food	
2	February 27.....	Guinea-pig	440 gm.	5 tablets	Mixed with food	
	February 25.....	Guinea-pig	440 gm.	5 tablets	Mixed with food	} Loss of weight; no sign of illness.
	February 26.....	Guinea-pig	440 gm.	5 tablets	Mixed with food	
3	February 27.....	Guinea-pig	450 gm.	5 tablets	Mixed with food	
	February 26.....	Guinea-pig	450 gm.	5 tablets	Mixed with food	} Same as in Experiment 2. ¹¹
4	February 27.....	Rabbit	1,000 gm.	3 tablets	Stomach tube	
	February 26.....	Rabbit	1,000 gm.	5 tablets	Stomach tube	
	February 27.....	Rabbit	1,000 gm.	5 tablets	Stomach tube	} Died 14 hours after last feeding. ¹²
5	February 28.....	Rabbit	1,500 gm.	6 gm. powder	Stomach tube	
	February 27.....	Rabbit	1,500 gm.	5 tablets	Stomach tube	
	March 1.....	Rabbit	1,500 gm.	5 tablets	Stomach tube	} Lost 25 gm. in weight; no other change
6	February 27.....	Rabbit	1,000 gm.	1 tablet	Subcutaneously	
7	March 2-8.....	Rabbit	2,110 gm.	1 tablet	Daily through stomach tube	

10. Each tablet was stated on the container to be equal to 15 grains in weight.

11. In Experiments 2 and 3, probably on account of the ill-tasting properties of the drug, the animals practically refused to eat the adulterated food, and the loss of weight was evidently in some degree due to partial starvation.

12. An autopsy was held on the rabbit of this experiment soon after it was found dead, and beyond a general tinting of the mucous membranes of the stomach and duodenum a yellow color of a tint comparable to that of the Chinosol, nothing of a pathologic nature was found.

Protocols of Cooper and Martin

ACTION OF CHINOSOL ON BACTERIA

STAPHYLOCOCCUS PYOGENES AUREUS, 24 HOURS' CULTURE

Exp.	Agent	Strength	—15 minutes—		—30 minutes—	
			Original	Duplicate	Original	Duplicate
1	Phenol	7:1000	+	+	+	+
2	Phenol	8:1000	+	+	+	—
3	Phenol	9:1000	+	—	—	—
4	Phenol	10:1000	—	—	—	—
5	Phenol	11:1000	—	—	—	—
6	Chinosol	80:1000	—	—	—	—
7	Chinosol	100:1000	—	—	—	—
8	Chinosol	120:1000	—	—	—	—
9	Chinosol	160:1000	—	—	—	—
10	Chinosol	200:1000	—	—	—	—

Thus none of the subcultures from the Chinosol dilutions grew. The dilution of the Chinosol in the broth tubes (10 c.c.) varied from

$$1 \text{ in } \frac{1000}{80} \times \frac{10}{.013} = 1 \text{ in } 9615 \text{ to } 1 \text{ in } \frac{1000}{200} \times \frac{10}{.013} = 1 \text{ in } 3846$$

one drop (.013 c.c.) being the amount subcultured from the dilutions into 10 c.c. broth. It was found, however, that a dilution of 1 in 100,000 inhibited staphylococci in broth while in 1 in 1,000,000 did not inhibit. The subcultures were, therefore, again subcultured into 10 c.c. so as to increase the dilution of Chinosol to well over 1 in 1,000,000, no inhibitory action then taking place; one drop (.013 c.c.) from each subculture being introduced into another broth-tube (10 c.c.).

The actual dilutions of Chinosol in the second series of subcultures varied between

$$1 \text{ in } 9615 \times \frac{10}{.013} = 1 \text{ in } 7,396,150$$

and

$$1 \text{ in } 3846 \times \frac{10}{.013} = 1 \text{ in } 2,958,460$$

All the subcultures *grew* under these conditions:

Agent	Strength	—15 minutes—		—30 minutes—	
		Original	Duplicate	Original	Duplicate
Chinosol	80:1000	+	+	+	+
Chinosol	100:1000	+	+	+	+
Chinosol	120:1000	+	+	+	+
Chinosol	160:1000	+	+	+	+
Chinosol	200:1000	+	+	+	+

As little time as possible was allowed to elapse between the two series of subcultures; about 30 minutes elapsed in the experiments.

BACILLUS TYPHOSUS, 24 HOURS' CULTURE

Agent.	Strength.	15 minutes.	
		Orig.	Dup.
Phenol	7:1000	+	+
Phenol	8:1000	+	—
Phenol	9:1000	—	—
Phenol	10:1000	—	—

Chinosol	120:1000	—	—
Chinosol	140:1000	—	—
Chinosol	160:1000	—	—
Chinosol	180:1000	—	—
Chinosol	200:1000	—	—

Chinosol	120:1000	+	+
Chinosol	140:1000	+	+
Chinosol	160:1000	+	+
Chinosol	180:1000	+	+
Chinosol	200:1000	+	+

First Series of Subcultures: Dilution of Chinosol in broth varying from:

$$1 \text{ in } \frac{1000}{120} \times \frac{10}{.013} = 1 \text{ in } 6410.$$

$$\text{to } 1 \text{ in } \frac{1000}{200} \times \frac{10}{.013} = 1 \text{ in } 3846.$$

Second Series of Subcultures: Dilutions of Chinosol varying from:

$$1 \text{ in } 6410 \times \frac{10}{.013} = 1 \text{ in } 4,930,770.$$

$$\text{to } 1 \text{ in } 3846 \times \frac{10}{.013} = 1 \text{ in } 2,958,460$$

Chinosol had less inhibitory action on *Bacillus typhosus* than on *Staphylococcus pyogenes aureus*, 1 in 5000 inhibiting the growth of *B. typhosus* and in 1 in 50,000 not inhibiting growth. A second series of subcultures were thus taken, as in the case of the *S. p. aureus*, so that the dilution of Chinosol was well above 1 in 50,000.

Probably the reason Chinosol gives a higher phenol-coëfficiency with *S. p. aureus* than with *B. typhosus* when inhibition is not allowed for, is because it exerts a greater inhibitory power on the former organism than on the latter one.

QUININ ARSENATE REFUSED RECOGNITION

Report of the Council on Pharmacy and Chemistry

(From The Journal A. M. A., July 16, 1910)

The advisability of admitting quinin arsenate as a non-proprietary article to New and Nonofficial Remedies was taken up for consideration by the Council and the product was referred to a committee on chemistry. This committee recommended that the opinion of the staff of clinical consultants should be obtained relative to the value of this product. This was done and on the staff's recommendation the drug was refused recognition and the Council ordered the following statements to be published.

W. A. PUCKNER, Secretary.

Quinin arsenate is the secondary quinin salt of arsenic acid. It contains 8 per cent. of elementary arsenic and 69 per cent. of anhydrous quinin, 0.1 gm. ($1\frac{1}{2}$ grains) would be equivalent to approximately .092 gm. ($1\frac{9}{20}$ grains) of quinin sulphate and to 0.032 gm. ($\frac{1}{2}$ grain) of sodium arsenate (five times the official dose). It is thus seen that the proportions of the two chief ingredients in the salt are such that an efficient dose of quinin cannot be given in this form without introducing a dangerous amount of arsenic. As it does not appear that this preparation possesses any properties that might not be found in a mixture of quinin salts and various preparations of arsenic, and as it has no advantage over other forms of arsenic now available, there is no reason for including it among unofficial non-proprietary remedies. Attempts to substitute it for other quinin salts would be likely to lead to overdosing with arsenic.

STRYCHNIN ARSENATE REFUSED RECOGNITION

Report of the Council on Pharmacy and Chemistry

(From *The Journal A. M. A.*, Sept. 24, 1910)

The Council, after considering the advisability of admitting to New and Nonofficial Remedies the unofficial, non-proprietary preparation, strychnin arsenate, decided not to admit it, and authorized publication of the following report.

W. A. PUCKNER, Secretary.

Strychnin arsenate is a compound of the alkaloid strychnin with arsenic acid, containing between 68 and 70 per cent. of anhydrous strychnin. It is a white, crystalline powder of small, colorless or faintly yellowish, transparent or slightly opaque prisms, or in white acicular crystals, odorless but extremely bitter. It is slowly soluble in about 20 parts of water at 25 C., more readily soluble in hot water, slightly soluble in alcohol, insoluble in chloroform or ether.

After considering the properties of this substance the Council voted not to accept it for N. N. R., as there is no sufficient reason for combining two powerful remedies in such form. As a chemical combination there appears to be no objection to it, as the compound is sufficiently definite, but the readiness with which the salt separates into its constituents, strychnin and arsenic acid, indicates that it can present no advantages over a mixture of its components so far as pharmacologic action and therapeutic use are concerned. On the other hand, it is both unscientific and irrational to pre-

scribe two such energetic remedies having quite different indications under such a fixed form that the efficient dose of one may involve an unsuitable and perhaps dangerous dose of the other.

If a dose of strychnin arsenate equivalent to 0.002 gm. (1/32 grain) of strychnin sulphate is given, the patient would receive about 0.00063 gm. (1/100 grain) of arsenic acid, which is about one-fifth the official dose. On the other hand, strychnin arsenate cannot be used to bring out the therapeutic effects of arsenic in cases in which it is necessary to push the latter remedy, because this would necessitate the giving of dangerous doses of strychnin. A much more appropriate and scientific procedure would be to prescribe the medicines separately or in an extemporaneous pill or solution in which the proportions of the two ingredients could be changed from time to time according to the varying indications in the particular case.

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